Brain and behavioural correlates of emotional voice processing in autism and its broader phenotype

Valerie Mei Zhi Yap

ORCID: 0000-0002-7425-3647

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Abstract

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterised by impairments in two core domains of social communication deficits and restricted, repetitive behaviours or interests. A milder variant of autism-like characteristics, known as the Broader Autism Phenotype (BAP), is present at higher rates in relatives of individuals with ASD than the general population, indicating a genetic liability for ASD. There is a wealth of social cognitive research documenting theory of mind, empathising, and emotional face processing deficits in ASD and the BAP, which correspond to abnormal brain function in the "social brain". However, less research has been conducted on the brain and behavioural correlates of emotional voice processing in ASD and the BAP, despite its significance for social cognition.

This thesis aimed to profile emotional voice processing abilities in ASD and the BAP in relatives and the general population, specifically relating to non-linguistic vocalisations known as vocal affect bursts (e.g., laughter, cries, screams). This thesis also aimed to identify the neurobiological substrates of emotional voice processing in individuals with ASD and relatives with the BAP. Three studies were performed to address these aims, each using the same purpose-built, web-based and/or functional MRI (fMRI) task to assess behavioural performance and elicit brain activation. Whole-brain activation elicited by the fMRI task was assessed using random- and fixed-effects analyses (RFX and FFX), which allowed inferences to be made on the population and sample levels, respectively.

Study 1 examined vocal affect burst recognition and its neurobiological correlates in individuals with high-functioning ASD (n = 16) compared to typically-developing controls (n = 16). The ASD group demonstrated a vocal emotion recognition deficit on the web-based task, where they misclassified neutral non-linguistic voices as expressing basic emotions at a

higher rate than controls. RFX analyses revealed no significant group differences in brain activation, whereas FFX analyses revealed that the ASD group demonstrated higher activation relative to controls in widely distributed regions associated with emotional voice processing, executive function, memory, motor and somatosensory processing, and visual processing. These findings enable atypical brain activation to be inferred for this specific ASD cohort, but not for the wider ASD population. Although cohort-specific, such information may facilitate hypothesis generation for future investigations of neurobiological compensation in ASD.

Study 2 addressed the same research questions as Study 1 in relatives of individuals with ASD (n = 13) who were determined to have the BAP on clinical assessment. The BAP group demonstrated no vocal emotion recognition deficit relative to controls (n = 13) on the web-based task. Under FFX analyses alone (not RFX analyses), the BAP group demonstrated significantly higher activation in the left lateral occipital cortex relative to controls. Inferences about the FFX findings are limited to the specific BAP cohort assessed here, and cannot be extended to the wider population of ASD-relatives with the BAP. Nonetheless, these findings may inform new hypotheses exploring endophenotypes (i.e., intermediate phenotypes) of ASD, characterised by a similar expression of neurobiological compensation in ASD and the BAP.

Study 3 used the web-based task to assess the association between vocal affect burst recognition and the continuous distribution of BAP traits in the general population of individuals without a family history of ASD. It was hypothesised that lower recognition accuracy for the six basic emotions would correlate with higher self-ratings of BAP traits. In contrast to expectations, higher classification accuracy (and emotional intensity ratings) for angry voices correlated significantly with *higher* self-ratings of rigid BAP traits. The specific anger-rigid association indicates that enhanced auditory threat detection constitutes an aspect

of the BAP in the general population. Further research is recommended to examine whether this relationship is mediated by underlying personality factors like neuroticism or trait anxiety.

Overall, different behavioural profiles of emotional voice processing abilities were observed in individuals with ASD (deficit—misclassifying neutral voices as being emotional), relatives with the BAP (no deficit—intact performance), and individuals from the general population with higher levels of BAP traits (advantage—enhanced sensitivity to angry voices). The neuroimaging findings of enhanced activation in the specific ASD and BAP cohorts assessed here may have implications for future research investigating the role of neurobiological compensation for emotional voice processing in their respective populations, potentially including the exploration of endophenotypes of ASD. Such studies would ideally include larger ASD and BAP (relatives) samples that enable the assessment of more homogenous, identifiable subgroups who may be susceptible to increased cognitive demands for emotional voice processing. This thesis extends research on social cognition within the voice modality in ASD and the BAP, and may have wider implications for understanding the genetic aetiology of social communication impairments in ASD.

Declaration

This is to certify that:

1. the thesis comprises only my original work towards the PhD except where indicated in the Preface,
2. due acknowledgement has been made in the text to all other material used,
3. the thesis is fewer than 100,000 words in length, exclusive of tables, figures, footnotes, references, and appendices.

_____

Valerie Yap

To my parents,

who have given me everything.

Acknowledgements

I am very excited to write this section of my thesis. I am writing it last, so it marks the end of a long journey that has challenged my intellect, confidence, and character to an extent I did not expect. I have many people to thank for supporting this research and for cheering me on towards the finish line.

I would like to thank **all participants** for volunteering in this study. Their goodwill to dedicate hours to participate in this research, with no guarantee of receiving any reward in return, has truly humbled me.

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♥

Academic Work and Awards

I. Academic Work to Arise from This Thesis

Publications in refereed journals

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Manuscripts in preparation

Yap, V. M. Z., Connelly, A., Green, C. C., Scheffer, I. E., & Wilson, S. J. (2019). Functional MRI Correlates of Recognising Non-Linguistic Vocal Emotions in Autism Spectrum Disorder.

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Instruments

Yap V. M. Z., McLachlan, N. M., & Wilson, S. J. Emotions and Me. [Computer Software]. URL: http://emotions.sollysweb.com/index_new.php.

Conference abstracts

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Yap, V. M. Z., McLachlan, N. M., Scheffer, I. E., & Wilson, S. J. (2015). Vocal emotion processing, empathy and features of the Broader Autism Phenotype. *Second Conference of the Australian Music and Psychology Society (AMPS);* Sydney, Australia.

Yap, V. M. Z., McLachlan, N. M., Scheffer, I. E., & Wilson, S. J. (2015). Vocal emotion processing, empathy and the Broader Autism Phenotype. *Music, Mind and Emotion Workshop*; Sydney, Australia.

Other presentations

Yap, V. M. Z., McLachlan, N. M., & Wilson, S. J. (2015). Individual differences in vocal emotion processing: Findings from the general population and implications for Autism Spectrum Disorder. *Australian Music & Psychology Society (AMPS) Seminar Series*; Melbourne, Australia. Invited speaker.

Wilson, S. J. & **Yap, V. M. Z.** (2015). Understanding emotions in the noises we make. *Collaborative Autism Study Barwon Celebration*; Geelong, Australia.

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II. Other Academic Work During the PhD Course

Publications in refereed journals

Green, C. C., Brown, N. J., **Yap, V. M. Z.**, Scheffer, I. E., & Wilson, S. J. (2019). Cognitive processes predicting advanced theory of mind in the broader autism phenotype. *Autism Research*. Advance online publication. doi:10.1002/aur.2209

Manuscripts in preparation

Ward, L. M. O., **Yap, M. Z. V.**, Wilson, S. J., & McLachlan, N. M. (2018). The Timbre of Emotion: Empirical Analyses of an Evolutionary Model of Human Nonverbal Vocal Communication.

Conference abstracts

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III. Awards

2018 **Student/Trainee Award**
International Society for Autism Research

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Australasian Society for Social and Affective Neuroscience

2015 **Interstate Conference Support**
Melbourne School of Psychological Sciences, The University of Melbourne

2014 **Outstanding Presenter Award (PhD Student Conference)**
Melbourne School of Psychological Sciences, The University of Melbourne

2012 **Melbourne International Fee Remission Scholarship**
Melbourne International Research Scholarship
The University of Melbourne

Preface

The PhD candidate prepared all chapters of this thesis. The candidate was supervised by Professors Sarah Wilson (primary supervisor), Alan Connelly, and Ingrid Scheffer. The candidate and all supervisors contributed to the conceptualisation of research questions, task design/methodology, data interpretation, and revision of this thesis. Research within this thesis was primarily supported by a grant awarded to Prof Sarah Wilson by the United States Department of Defense (W81XWH-12-1-0490).

All behavioural and neuroimaging data were collected by the candidate. The candidate recruited participants with ASD (Study 1; Chapter 5) and family members with the BAP (Study 2; Chapter 6) from a larger database of participants enrolled in genetic research with the Collaborative Autism Study (CATS) at The University of Melbourne. The candidate received some assistance from Dr Cherie Green (postdoctoral research fellow from the CATS) to ascertain diagnosis in participants with ASD recruited for Study 1. Prior to their recruitment to Study 2, family members were determined to have BAP-positive status on formal assessment carried out by other clinicians and researchers (not the candidate) from the CATS team (e.g., Dr Cherie Green, Dr Natasha Brown, Prof Sarah Wilson, Prof Ingrid Scheffer).

The candidate designed a web-based task (part of an online program: "Emotions and Me", Yap, Solly, McLachlan, & Wilson, 2013; see Appendix A for a description of the software) and fMRI task for the collection of behavioural and neuroimaging data. The web-based task was programmed by an external contractor (Mr Mark Solly), and the fMRI task was programmed by the candidate. The candidate conducted all behavioural and neuroimaging analyses for Studies 1-3 (Chapters 5-7), including the pre-processing of fMRI data.

Chapter 7 (Study 3) comprises a published manuscript. Co-authors include two of the candidate's supervisors (Professors Sarah Wilson and Ingrid Scheffer) and a collaborator from the Melbourne School of Psychological Sciences at the University of Melbourne (Dr Neil McLachlan). All co-authors provided signed consent for the published manuscript in Chapter 7 to be included in this thesis and certified that the candidate is the primary author, having contributed 65% of content to the manuscript. The citation for the published manuscript is as follows:

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Abbreviations

AAL = Automated Anatomical Labelling

ACC = anterior cingulate cortex

ADHD = Attention-Deficit/Hyperactivity Disorder

ADI-R = Autism Diagnostic Interview-Revised

ADOS = Autism Diagnostic Observation Schedule

AQ = Autism Spectrum Quotient

ANOVA = analysis of variance

AS = Asperger's Syndrome

ASD = Autism Spectrum Disorder

BAP = Broader Autism Phenotype

BAPQ = Broader Autism Phenotype Questionnaire

CAM = Cambridge Mindreading Face-Voice Battery

CARS = Childhood Autism Rating Scale

CATS = Collaborative Autism Study

CNVs = copy number variants

DLPFC = dorsolateral prefrontal cortex

DSM = Diagnostic and Statistical Manual of Mental Disorders

DTI = diffusion tensor imaging

EEG = electroencephalography

EMG = electromyography

EPI = echo-planar imaging

EQ = Empathy Quotient

ERP = event-related potential

F0 = fundamental frequency

F1 = first formant

F2 = second formant

FFA = fusiform face area

FFX = fixed-effects analysis

fMRI = functional magnetic resonance imaging

FOV = field of view

FWE = family-wise error

GLM = general linear model

HFA = High-Functioning Autism

HRF = haemodynamic response function

ICD-10 = International Classification of Diseases, 10th Edition

IFG = inferior frontal gyrus

IOG = inferior occipital gyrus

IPL = inferior parietal lobule

IRI = Interpersonal Reactivity Index

LFA = Low-Functioning Autism

MAV = Montreal Affective Voices

MCC = middle cingulate cortex

MEG = magnetoencephalography

MNI = Montreal Neurological Institute

MNS = mirror neuron system

mPFC = medial prefrontal cortex

MTG = middle temporal gyrus

OFC = orbitofrontal cortex

PCC = posterior cingulate cortex

PDD = Pervasive Developmental Disorders

PDD-NOS = Pervasive Developmental Disorders, Not Specified

PET = positron emission topography

RFX = random-effects analysis

ROI = region-of-interest

SMA = supplementary motor area

SPM = Statistical Parametric Mapping

SQ = Systemising Quotient

SRS = Social Responsiveness Scale

STG = superior temporal gyrus

STS = superior temporal sulcus

TE = echo time

TMS = transcranial magnetic stimulation

CHAPTER 1

Thesis Overview

1.1. Background and Research Aims

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterised by impairments in two core domains of social communication deficits and restricted, repetitive behaviours or interests. The complete aetiology of ASD is unknown, although high heritability rates indicate a strong genetic component for the disorder (Ramaswami & Geschwind, 2018). Milder manifestations of autism-like characteristics are more prevalent in relatives of individuals with ASD compared to the general population, providing further support for a genetic basis of ASD (Sucksmith, Roth, & Hoekstra, 2011). These sub-clinical traits are collectively referred to as the Broader Autism Phenotype (BAP) and represent intermediate phenotypes, or endophenotypes, of ASD (Persico & Sacco, 2014). Chapter 2 provides an overview of the classification and epidemiology of ASD and the BAP.

Studies have shown that relative to controls, individuals with ASD and their family members demonstrate reduced social cognition on behavioural tasks and atypical activation within the "social brain", a widely distributed network of brain regions which specialise in social information processing (Chapter 3). Among other functions, social cognition allows us to understand the mental and emotional states of others through conceptual reasoning and more automatic simulation processes (Happé, Cook, & Bird, 2017). The "theory of mind" and "empathising-systemising" hypotheses of ASD account for difficulties in social cognition observed in individuals with ASD (Baron-Cohen, 2000, 2009). Social cognitive difficulties in ASD and the BAP are often assessed in the facial domain, with research showing a range of face processing abnormalities, including the recognition of emotional states (Uljarevic & Hamilton, 2013).

Social cognitive research within the voice domain has received less attention than the face. Nevertheless, vocal cues have some advantages for emotional communication, including their ability to signal emotional states over long distances and elicit attention in the absence of visual information. Current behavioural research on abnormalities in emotional voice processing in ASD is largely restricted to the recognition of emotional prosody ("tone of voice") or paralinguistic cues of emotion in speech (Chapter 4). A small number of neuroimaging studies has revealed atypical brain function related to the processing of emotional speech prosody in ASD (Eigsti, Schuh, Mencl, Schultz, & Paul, 2012; Gebauer, Skewes, Hørlyck, & Vuust, 2014; Rosenblau, Kliemann, Dziobek, & Heekeren, 2017). There is also some behavioural evidence for reduced recognition of emotional speech prosody in family members of affected individuals (Oerlemans et al., 2014; Tajmirriyahi, Nejati, Pouretemad, & Sepehr, 2013), although this process has not been examined using neuroimaging methods.

This thesis seeks to extend behavioural and neuroimaging research on emotional voice processing in ASD and the BAP using alternative stimuli, specifically non-linguistic vocalisations known as vocal affect bursts (e.g., laughter, screams, cries). Vocal affect bursts are considered to be less conventionalised and arise primarily from physiological factors rather than cultural influences (Scherer, 1994). They are generally more recognisable than emotional speech prosody (Hawk, Van Kleef, Fischer, & Van Der Schalk, 2009). They may serve an advantage for research targeting purer behavioural and neurobiological markers of emotional voice processing, since they exclude the confounds of language processing inherent to speech-embedded prosody.

The overarching aim of this thesis can be divided into two primary research questions, addressed across three studies (Figure 1.1). In addition to their contributions to the social

cognitive literature in ASD, these questions may have wider implications for genetic research into the biological pathways underlying ASD:

1. What is the profile of emotional voice processing abilities in ASD, the BAP in relatives, and the distribution of BAP traits in the general population?
2. What are the neurobiological substrates of emotional voice processing in individuals with ASD and relatives with the BAP?

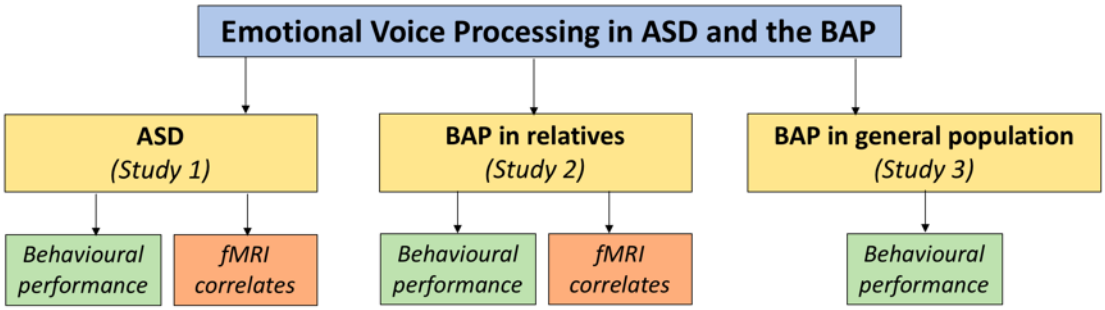


Figure 1.1. Flowchart of the three studies in relation to the thesis aims.

1.2. Study Design and Key Findings

We designed a behavioural, web-based task to assess the recognition of vocal affect bursts of the six basic emotions (i.e., anger, disgust, fear, happiness, sadness, surprise) and non-linguistic neutral vocalisations in all three studies. The web-based task required participants to classify each vocal stimulus into one of seven forced-choice categories (e.g., six emotions and neutral category) and rate the intensity of emotional stimuli. We also designed a functional MRI (fMRI) task to elicit brain activation associated with the recognition of the same vocal affect bursts in Studies 1 and 2. The fMRI task consisted of active blocks (condition of interest), which required participants to classify vocal affect bursts into one of two forced-choice basic emotion categories. Active blocks were contrasted to baseline blocks (control condition), which required participants to classify non-linguistic neutral vocalisations into one of two gender categories (i.e., male/female). Random- and fixed-effects analyses (RFX and FFX)

were performed to determine whole-brain activation in each group, and to compare differences between groups, in order for inferences to be made at the population and sample levels, respectively (Friston, Holmes, & Worsley, 1999; Penny & Holmes, 2003).

Study 1 (Chapter 5) examined vocal affect burst recognition and its neural correlates in adolescents and adults with high-functioning ASD (IQ > 70; n = 16) compared to healthy controls matched on sex, age, and IQ (n = 16). Controls reported having no first-degree relatives with ASD and were screened for the BAP (i.e., BAP-negative status) using the Broad Autism Phenotype Questionnaire (BAPQ). The ASD group demonstrated a vocal emotion recognition deficit on behavioural testing by misclassifying neutral stimuli into basic emotion categories at higher rates than controls. RFX analyses of the fMRI data revealed no significant group differences in whole-brain activation, whereas FFX analyses revealed that the ASD group showed higher activation than controls in regions serving emotional voice processing, executive function, memory, motor and somatosensory processing, and visual processing. Based on these findings, atypical brain activation underlying vocal emotion recognition can only be inferred for the specific cohort of ASD participants assessed here, but cannot be generalised to the wider ASD population. These findings may have implications for future research examining the role of neurobiological compensation on emotional voice processing in ASD.

Study 2 (Chapter 6) examined vocal affect burst recognition and its neural correlates in adult relatives of individuals with ASD (n = 13) compared to matched controls without a family history of ASD (n = 13). Family members mainly consisted of first-degree relatives and a small number of second-degree relatives from different multiplex families. Prior to recruitment, all relatives were determined to have the BAP (i.e., BAP-positive) on extensive

cognitive and behavioural assessment, whereas controls were screened for the BAP on the BAPQ. The BAP group (ASD-relatives) showed no vocal emotion recognition deficit on behavioural testing, classifying neutral and emotional stimuli into their respective categories as accurately as controls. As per Study 1, significant group differences in whole-brain activation were revealed under the FFX model alone (not RFX), indicating atypical activation for vocal emotion recognition specific to this cohort of ASD-relatives with the BAP. Specifically, the FFX analyses revealed higher activation for the BAP group relative to controls in the left lateral occipital cortex alone (also enhanced in the ASD group from Study 1).

Study 3 (Chapter 7) was a purely behavioural study, which measured associations between vocal affect burst recognition and self-ratings of BAP traits on the BAPQ in adults without a family history of ASD (n = 61). Participants were not grouped according to BAP-positive or BAP-negative status, but rather, the continuous distribution of BAP traits across the sample was analysed. Although it was hypothesised that lower performance on the web-based task would correlate with higher levels of BAP traits, a significant effect appeared in the opposite direction. Specifically, higher classification accuracy and emotional intensity ratings for angry voices correlated with *higher* levels of BAP traits for rigidity. These findings suggest that BAP traits are associated with heightened sensitivity to auditory threat signals in individuals who do not have a genetic susceptibility to ASD. These findings also suggest the potential role of "Big Five" personality factors (e.g., neuroticism) and trait anxiety for mediating the anger-rigid relationship in the general population, as these factors are associated with the BAP and attentional bias towards negative environmental stimuli.

1.3. Conclusions

Behavioural findings from the three studies revealed different profiles of emotional voice processing abilities in ASD and the BAP: (i) individuals with ASD demonstrated a recognition

deficit (i.e., misclassifying neutral stimuli into basic emotion categories), (ii) relatives with BAP-positive status demonstrated *no deficit*, and (iii) individuals from the general population with higher levels of BAP traits demonstrated *heightened sensitivity* specific to angry voices. These findings indicate that deficits in vocal emotion recognition are unique to ASD and do not extend to the BAP in relatives and the general population. These findings also offer new insights into the nature of the BAP in the general population.

Neuroimaging findings from the first two studies revealed atypical brain activation for emotional voice processing specific to the ASD participants and BAP relatives assessed here. Under the FFX model, the two groups demonstrated enhanced brain activation compared to their respective control groups, suggesting the possibility that they relied on additional cognitive resources and compensatory mechanisms to recognise vocal emotions. Importantly, the BAP group showed a similar, but less extensive, profile of atypical brain activation relative to the ASD group. These findings may inform the generation of new hypotheses exploring endophenotypic markers of ASD, characterised by a milder expression of neurobiological compensation for emotional voice processing in relatives with the BAP compared to individuals with ASD.

Overall, this thesis extends research on emotional voice processing in ASD and the BAP. A strength of this thesis includes consistency in task design to address the aims (e.g., same vocal stimuli, behavioural, and fMRI tasks), which ultimately allowed inferences made from each study to be discussed in the context of the other findings. Implications of the behavioural and neuroimaging findings are discussed further in Chapter 8. Directions for future research are also addressed.

CHAPTER 2

Autism Spectrum Disorder and Its Broader Phenotype

Overview: This chapter provides a broad overview of the definition and epidemiology of Autism Spectrum Disorder (ASD) and the Broader Autism Phenotype (BAP). It reviews how concepts of ASD have evolved over time and highlights the heterogeneity of symptoms and aetiological factors that constitute the disorder. It also describes how studying the BAP in families with ASD supports an endophenotypic approach towards gene discovery in ASD.

2.1. Historical Concepts

The term "autism" originates from the Greek word "autos" or "self" (Lombardo & Baron-Cohen, 2010). It was introduced in 1910 by psychiatrist, Eugen Blueler, to describe the "inner life" of patients with schizophrenia, characterised by fantasy and a withdrawal from the external world (Evans, 2013; Kuhn & Cahn, 2004). The view of autism as a form of psychosis was popular among psychiatrists between the 1920s to 1950s, including Leo Kanner, who is widely credited for first considering autism as a diagnostic category (Evans, 2013; Verhoeff, 2013). In 1943, Kanner published detailed case studies on eight boys and three girls who demonstrated a "powerful desire for aloneness and sameness" (Kanner, 1943, p. 44), as characterised by significantly reduced social engagement, emotional detachment, intense fixations on routines, and limited spontaneous behaviour. Kanner observed that the children preferred contact with objects over human interaction—likely because objects retain fixed properties and do not disrupt one's solitude—and showed a persistent lack of responsiveness or aversion to the approach of others. They became highly anxious and distressed with changes to routine, discontinuity of patterns or things left incomplete. Kanner also observed that the children had delayed (or absent) language development, which was not used flexibly for the purposes of reciprocal social communication (pragmatic functions) but confined to echolalia, the recital of learned speech or for gratifying their own needs. He considered that this syndrome of "early infantile autism" may be an early form of childhood schizophrenia, where "extreme autistic aloneness" (Kanner, 1943, p. 242) was innate at birth rather than acquired after a period of normal development.

Since Kanner's seminal work, several changes have been made to the concept and definition of autism (Evans, 2013; Verhoeff, 2013; Wolff, 2004). Associations between autism and childhood schizophrenia were challenged with the rise of empirical research in the 1960s,

which, as reviewed by Rutter (1968), revealed that both conditions differed by age of onset (e.g., psychosis unlikely to arise in infancy), course (e.g., steadier course in autism without remissions or relapses), sex ratio (e.g., high male to female ratio in autism), associated symptoms (e.g., higher prevalence of intellectual disability and lower rates of delusions or hallucinations in autism), and family history (e.g., rare occurrence of schizophrenia in parents of children with autism). During this time, research interests also shifted towards deficits in language (e.g., speech and comprehension problems), cognitive function (e.g., intellectual disability, poor abstract reasoning, cognitive inflexibility), and sensory processing (e.g., poor visual perception and integration of multisensory information), which were often observed among children with autism (Frith, 1970a, 1970b; Lockyer & Rutter, 1970; Rutter, 1978; Tubbs, 1966; Wing & Wing, 1971). Some researchers even hypothesised that autism was primarily a disorder of language and cognition from which social withdrawal and behavioural abnormalities result as secondary symptoms (Rutter, 1968; Rutter & Bartak, 1971).

New insight into autism emerged from an epidemiological study on intellectually disabled children, which showed that those with impaired reciprocal social interaction were more likely to have abnormal verbal and nonverbal communication skills (e.g., poor language comprehension, idiosyncratic speech, inappropriate use of gestures, odd intonation) and repetitive behaviours (at the expense of imaginative or symbolic play) compared to those without social impairments (Wing & Gould, 1979). This led the authors to conceptualise autism as a "triad of social and language impairment" (Wing, 1981b, p. 37)—or a cluster of deficits in social interaction, communication, and imaginative activities or repetitive, stereotyped behaviours—which may be associated with early developmental abnormalities to brain structure and function. Wing observed that the triad of impairments varied in severity

across intelligence levels, where children with more pronounced intellectual disability were more aloof and indifferent to others (Wing, 1981b).

Wing also observed that the triad was present in a minority of individuals with normal intellect (Wing, 1981a, 1981b) and drew parallels between her cases and Hans Asperger's (Asperger, 1944) early clinical accounts of "autistic psychopathy" in four intelligent children. Unlike the children with autism described around the same time by Kanner (1943), the children observed by Asperger had normal speech development and special interests in unusual topics (e.g., bus schedules, history of trains, astronomy) which often dominated their conversation. They appeared to be less emotionally withdrawn and more interested in social engagement, although they struggled to apply the appropriate social conventions when approaching or responding to others. They demonstrated poor pragmatic language skills (e.g., pedantic, one-sided or repetitive speech), difficulties with nonverbal communication (e.g., odd intonation, restricted use and poor understanding of facial expressions and gestures), insistence on sameness (e.g., attachment to objects, routines), and stereotyped movements. Accordingly, Wing (1981a) introduced the term "Asperger's Syndrome" to account for individuals "who have autistic features but who talk grammatically and who are not socially aloof" (p. 124). She suggested that Asperger's Syndrome and autism may be classified as sub-groups under a broader category of disorders which share the same triad of impairments (Wing, 1981a), although this classification was only formalised more than a decade later in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, [APA], 1994).

2.2. Diagnostic Criteria

2.2.1. Previous criteria

Formal diagnostic criteria for autism first appeared under the broader category of "Pervasive Developmental Disorders (PDD)" in the third edition of the DSM (DSM-III; APA, 1980) and were updated seven years later in the revised edition (DSM-III-R; APA, 1987). Unlike the DSM-III, which adopted Kanner's (1943) and Rutter's (1978) label of "Infantile Autism", the DSM-III-R used the label "Autistic Disorder" and loosened criteria of onset from strictly before 30 months to anytime during infancy or childhood. The DSM-III-R specified three core domains of impairment for Autistic Disorder, which reflected the triad proposed by Wing and Gould (1979). Sixteen symptoms were specified across the three domains (e.g., abnormal play, inability to form friendships, abnormalities in production or content of speech, inability to initiate or sustain conversation, restricted range of interests, stereotyped body movements), and individuals were required to have one to two symptoms per domain to meet diagnostic criteria. Those with poor reciprocal social interaction and communication skills who did not meet criteria for Autistic Disorder would fall under a separate PDD subgroup of "Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS)".

Diagnostic criteria for Autistic Disorder and subgrouping of PDDs were revised further in the DSM-IV (1994) to allow greater diagnostic specificity and more consistency with autism criteria provided under another diagnostic system known as the International Classification of Diseases, 10th Edition (ICD-10; World Health Organization, 1992). In the DSM-IV, Autistic Disorder was still defined by the three core domains (e.g., qualitative impairment in social interaction, communication, and restricted, repetitive behaviours/interests), but with age of onset restricted to before three years. The DSM-IV retained the subgroup of PDD-NOS, but like the ICD-10, included additional PDD subgroups, most notably "Asperger's Disorder",

which is commonly referred to using Wing's (1981) term of Asperger's Syndrome (AS). The inclusion of AS was controversial, as it shares similar impairments in reciprocal social interaction and repetitive behaviours with Autistic Disorder, but has relatively normal development of language, cognitive skills, and adaptive behaviour in other aspects besides social interaction (Sanders, 2009; Volkmar, 1998). AS was particularly confused with "High-Functioning Autism (HFA)", a term which is not listed in any edition of the DSM but is frequently used by clinicians and researchers to describe individuals with Autistic Disorder who have an IQ above 70, despite language delay (Ghaziuddin & Mountain-Kimchi, 2004; Kamp-Becker et al., 2010; Noterdaeme, Wriedt, & Höhne, 2010). Some suggested that AS and Autistic Disorder should be re-classified as dimensional variants of the same condition, characterised primarily by social impairment (Kamp-Becker et al., 2010; Tryon, Mayes, Rhodes, & Waldo, 2006; Wing, 2005).

2.2.2. Current criteria

Major revisions to incorporate the dimensional structure of autism were made in the fifth, most recent edition of the DSM (DSM-5; APA, 2013). The PDD subgroups of Autistic Disorder, Asperger's Disorder, and PDD-NOS were collapsed under the broad diagnostic category of "Autism Spectrum Disorder (ASD)". The three core domains of impairment were merged into two: (a) persistent deficits in social communication and social interaction across multiple contexts and (b) restricted, repetitive patterns of behaviour, interests, or activities. As outlined in Figure 2.1, individuals must meet a number of symptom classifiers under each domain to qualify for a diagnosis of ASD.

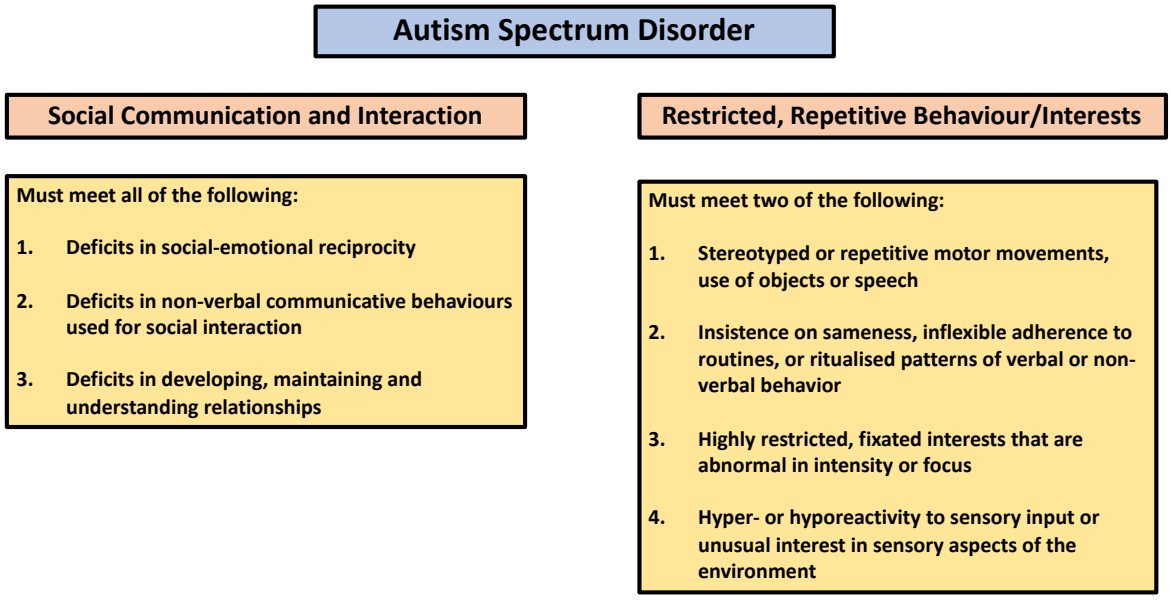


Figure 2.1. Two core domains of impairment (with corresponding symptom classifiers) that characterise ASD, as described in the DSM-5.

Symptoms of ASD may be confirmed on clinical assessment or by accounts of developmental history and behaviour in social or home environments. Symptoms should not be better explained by intellectual disability or global developmental delay, although the presence or absence of intellectual and language impairment should be specified. Other comorbidities (e.g., medical, genetic, neurodevelopmental, mental, or behavioural conditions) should also be specified where present. The DSM-5 does not provide a minimum cut-off for age of onset, but states that symptoms must emerge in the "early developmental period". However, it acknowledges that social impairments may not become obvious until "social demands exceed limited capacities" (APA, 2013) and that symptoms may be more difficult to detect later in life as individuals acquire strategies to compensate for their deficits. Importantly, the two core domains of impairments must cause significant impairment to the individual's adaptive functioning (e.g., social, occupational) and should each be assigned severity ratings according to three levels of support (Figure 2.2).

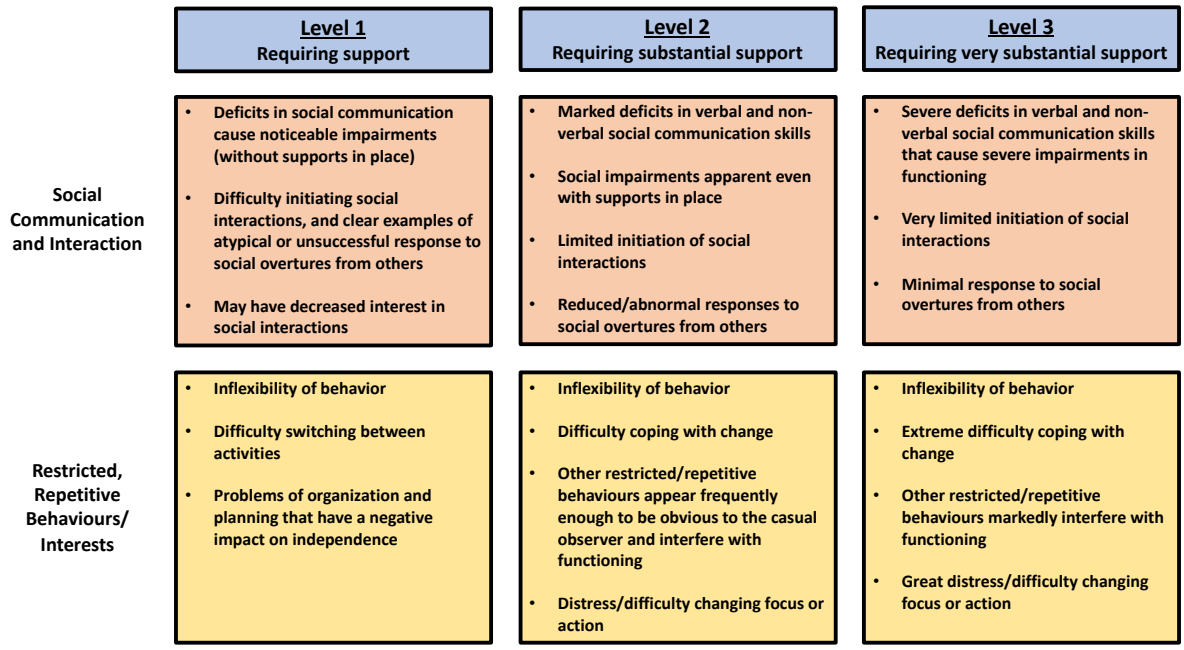


Figure 2.2. Severity specifiers provided by the DSM-5 to characterise the impact of the two ASD domains on adaptive functioning.

Research has shown that between 60-90% of individuals with a DSM-IV diagnostic label of Autistic Disorder, AS, or PDD-NOS meet DSM-5 criteria for ASD (Huerta, Bishop, Duncan, Hus, & Lord, 2012; Maenner et al., 2014; McPartland, Reichow, & Volkmar, 2012). Among subgroups, those with Autistic Disorder or intellectual disability are more likely to meet DSM-5 criteria than those with AS, PDD-NOS, or normal intellect (Maenner et al., 2014; McPartland et al., 2012). A meta-analysis that compared the frequency of ASD diagnoses based on DSM-IV and DSM-5 criteria showed a greater reduction of cases for PDD-NOS than Autistic Disorder (i.e., 70% compared to 20% reduction) under the new classification (Kulage, Smaldone, & Cohn, 2014). The DSM-5 recommends that individuals with deficits in social communication who fail to meet ASD criteria (i.e., no restricted, repetitive behaviours) should be evaluated for a diagnosis of "Social (Pragmatic) Communication Disorder" instead. This diagnostic category was newly introduced to provide a "safety-net diagnosis" for individuals with PDD-NOS, although existing studies show that it only accounts for a small percentage who do not meet ASD criteria (Kulage et al., 2014).

2.2.3. Diagnostic measures

Clinical evaluation of ASD should be based on a developmental framework to characterise delays and deficits in the acquisition of social skills, language and communication, cognitive functions, sensorimotor skills, and unusual behaviours and interests (Lai, Lombardo, & Baron-Cohen, 2014). Information related to the individual's behavioural presentation should be gathered from multiple sources and contexts (e.g., parents/teachers for home/school), including the examiner's own interaction with the individual in a semi-structured clinical setting (Ozonoff, Goodlin-Jones, & Solomon, 2005). A multidisciplinary team approach is ideal, with medical (e.g., paediatrician, psychiatrist) and allied health professionals (e.g., psychologist, speech pathologist) contributing expert opinion to the diagnosis (Falkmer, Anderson, Falkmer, & Horlin, 2013; Ozonoff et al., 2005).

A number of diagnostic measures and screening tools have been used to assess ASD (Table 2.1). The "gold-standard" diagnostic measures are the Autism Diagnostic Observation Schedule (ADOS-G and ADOS-2; Lord et al., 1999; Lord et al., 2012) and the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994), which have a high classification rate of 0.84-0.88 when used together (Falkmer et al., 2013). The ADOS is a semi-structured interactive assessment of ASD symptoms, which includes five separate modules tailored to different age groups and levels of expressive language (e.g., toddler to adults). Each module consists of standardised activities and "presses" that allow the individual to engage in social interaction and communication (e.g., opportunities for subjects to initiate and participate in play or conversation). Behaviour is rated on an extensive list of items like stereotyped/idiosyncratic use of words or phrases, unusual eye contact, spontaneous initiation of joint attention, quality of social overtures and social response, facial expressions directed to

examiner, hand/finger/other complex mannerisms, and excessive interest in unusual or highly specific topics/objects. Revised algorithms for all modules in the ADOS-2 are divided into two domains, "Social Affect" (social interaction plus communication) and "Restricted and Repetitive Behaviours", as consistent with the DSM-5 classification for ASD (Hus & Lord, 2014; Lord et al., 2012). Cut-off values on the combined total score are indicated for overall diagnosis (i.e., non-spectrum, autism spectrum, autism) and ASD severity (i.e., minimal-to-no evidence, low, moderate, high).

The ADI-R is a semi-structured, comprehensive caregiver interview about an individual's developmental history and current behaviour (Lord, Rutter, & Couteur, 1994). It is used to establish a diagnosis of ASD in children and adults with mental ages from 18 months and above. It generates algorithm scores for the three symptom domains of reciprocal social interaction (e.g., smiling and responding to others, offering and seeking comfort), communication and language (e.g., delayed language, stereotyped utterances), and restricted/repetitive behaviours and interests (e.g., unusual preoccupations and sensory interests, hand/finger mannerisms), as consistent with the DSM-IV and ICD-10 classification for ASD. To qualify for a diagnosis of ASD, the individual should meet cut-off scores for each domain and should have demonstrated abnormalities in at least one domain by 36 months of age.

Table 2.1

List of Diagnostic and Screening Tools for ASD

Measure	Reference
Interview (diagnostic)	
Autism Diagnostic Interview-Revised (ADI-R)	Lord, Rutter, and Le Couteur (1994)
The Diagnostic Interview for Social and Communication Disorders (DISCO)	Wing, Leekam, Libby, Gould, and Larcombe (2002)
The Developmental, Dimensional and Diagnostic Interview (3Di)	Skuse et al. (2004)
Direct Observation (diagnostic)	
The Autism Diagnostic Observation Schedule (ADOS-G, ADOS-2)	Lord et al. (1999), Lord et al. (2012)
Childhood Autism Rating Scale (CARS, CARS-2)	Schopler, Reichler, and Rochen Renner (1988); Schopler, van Bourgondien, Wellman, and Love (2010)
Questionnaires (screening)	
Autism Spectrum Quotient (AQ)	Baron-Cohen, Wheelwright, Skinner, Martin, and Clubley (2001)
Autism Spectrum Screening Questionnaire (ASSQ)	Ehlers, Gillberg, and Wing (1999)
Checklist for Autism in Toddlers (CHAT, M-CHAT)	Baron-Cohen, Allen, and Gillberg (1992); Robins, Fein, Barton, and Green (2001)
Childhood Autism Screening Test (CAST)	Scott, Baron-Cohen, Bolton, and Brayne (2002)
Early Screening of Autistic Traits (ESAT)	Swinkels et al. (2006)
Infant Toddler Checklist (ITC)	Wetherby and Prizant (2002)
Quantitative Checklist for Autism in Toddlers (Q-CHAT)	Allison et al. (2008)
Social Responsiveness Scale (SRS, SRS-2)	Constantino (2002), Constantino and Gruber (2012)
The Ritvo Autism Asperger Diagnostic Scale (RAADS, RAADS-R)	Ritvo et al. (2008); Ritvo et al. (2011)

2.3. Epidemiology

2.3.1. Prevalence

The prevalence of ASD has been widely examined since the 1960s, with estimates ranging from 0.7 to 72.6 per 10,000 (Fombonne, 2003). Several variables can influence prevalence estimates, including geographical region (e.g., across countries, urban/rural locations), patient demographics (e.g., age, race), procedures for case identification (e.g., special education database vs. national registry, population-based screening vs. standardised in-depth assessment, DSM-IV vs. ICD-10 criteria), and sample size (Saracino, Noseworthy, Steiman, Reisinger, & Fombonne, 2010; Williams, Higgins, & Brayne, 2006). Despite the heterogeneity among studies, a general rise in prevalence has been reported over time, due in part to changes in nosology (e.g., broadening diagnostic criteria from DSM-III-R to DSM-IV) and increased public awareness of ASD (Matson & Kozlowski, 2011; Newschaffer et al., 2007; Randall et al., 2016).

The most recent global prevalence estimates for ASD were established by Baxter et al. (2015) based on data published from 18 countries between 1980 and 2009. Their systematic review included samples of people up to 27 years of age who met DSM (i.e., any version prior to DSM-5) and ICD-10 criteria for Autistic Disorder, AS or PDD-NOS. The authors reported an overall ASD global prevalence rate of 7.6 per 1000 (1 in 132 people). Between ASD sub-types, lower prevalence for Autistic Disorder (2.4 per 1000) was reported compared to AS and PDD-NOS combined (5.1 per 1000). Sex differences were significant, with a male-to-female ratio of 3:1 for Autistic Disorder and 4:1 for other ASDs. Baxter et al. (2015) also reported that among mental disorders worldwide, ASD was the leading cause of disability for children younger than 5 years and the fourth-highest cause of disability in children aged between 5-18 years, accounting for approximately 111 disability-adjusted life-years per 100,000.

Global prevalence estimates have not been established under DSM-5 criteria for ASD, although it may attenuate the trend for rising ASD prevalence given its decreased sensitivity and increased specificity (Baio et al., 2018; Burns & Matson, 2017; Maenner et al., 2014). Consistent with this view, a population-based study on Australian children showed that the incidence of ASD increased between 2010 and 2013 (i.e., from 20 to 34.2 per 10,000) but plateaued between 2013 and 2015, coinciding with the introduction of DSM-5 criteria at the time (Bent, Barbaro, & Dissanayake, 2017). For ASD sub-types, the authors reported a sharp decrease in the incidence of AS and PDD-NOS between 2012 and 2015 (i.e., from 4.7 to 0.2 and 5.6 to 0.5 per 10,000, respectively), despite an increase in the incidence of Autistic Disorder between 2010 and 2014. Similar findings were reported in a clinic-based study on American children, which found lower rates of ASD between 2013 and 2015 (39%) than between 2010 and 2013 (50%; Hartley-McAndrew, Mertz, Hoffman, & Crawford, 2016).

2.3.2. Prognosis

ASD is considered a lifelong condition, with poor long-term outcome and low quality of life expected in the majority of individuals (Steinhausen, Mohr Jensen, & Lauritsen, 2016; van Heijst & Geurts, 2015). Most individuals continue to have difficulties with social integration, securing employment, and living independently in adulthood (Howlin & Magiati, 2017). One systematic review on longitudinal studies in ASD from childhood to adulthood revealed that social functioning, cognitive ability, and language skills remained stable or declined over time, while adaptive functioning generally improved (Magiati, Tay, & Howlin, 2014). Predictors of long-term outcome in ASD include IQ, language abilities, and symptom severity in childhood (Gillespie-Lynch et al., 2012; Howlin & Magiati, 2017; Magiati et al., 2014). Other prognostic indicators include early diagnosis and early intense intervention (Estes et al., 2015;

Granpeesheh, Dixon, Tarbox, Kaplan, & Wilke, 2009; Virués-Ortega, Rodríguez, & Yu, 2013), as well as family factors like parenting stress and the quality of the mother-child relationship (Osborne, McHugh, Saunders, & Reed, 2008; Woodman, Smith, Greenberg, & Mailick, 2015).

2.3.3. Comorbidity

Over 70% of individuals with ASD have comorbid developmental, medical, or psychiatric conditions, which contribute to symptom severity and difficulties with adaptive functioning (Lai et al., 2014). Intellectual disability often co-occurs with ASD, with prevalence for comorbidity ranging from 16-70% across studies (De Bildt, Sytema, Kraijer, & Minderaa, 2005; Fombonne, 2003; Postorino et al., 2016; Tonnsen et al., 2016). Epilepsy also occurs at higher rates in ASD than the general population (e.g., 5-38%), and affected individuals with intellectual disability are at higher risk of developing epilepsy compared to those with normal intellect (Duerden et al., 2012; Frye, 2016; McTiernan, Leader, Healy, & Mannion, 2011; Tonnsen et al., 2016). ASD, intellectual disability and epilepsy may be associated through common genetic pathways, and may be due to monogenic disorders like Fragile X Syndrome, Rett's Disorder, Tuberous Sclerosis, and Angelman's Syndrome (Berry-Kravis, 2002; Glaze et al., 2010; Jeyabalan & Clement, 2016; Kotulska & Jóźwiak, 2011; Vissers, Gilissen, & Veltman, 2016). Other common physical comorbidities in ASD include sleep disturbance (e.g., insomnia, frequent night waking, shorter sleep duration; Cortesi, Giannotti, Ivanenko, & Johnson, 2010), gastrointestinal dysfunction (e.g., abdominal pain, constipation, diarrhoea; McElhanon, McCracken, Karpen, & Sharp, 2014), and motor impairments (e.g., hypotonia, toe-walking, poor fine and gross motor skills, coordination difficulties; Fournier, Hass, Naik, Lodha, & Cauraugh, 2010; Ming, Brimacombe, & Wagner, 2007).

Psychiatric comorbidities like depression, anxiety, and Attention-Deficit/Hyperactivity Disorder (ADHD) are consistently observed in ASD across age groups (e.g., children, adolescents, adults), regardless of intellectual ability (Joshi et al., 2013; Simonoff et al., 2008; Strang et al., 2012). A recent meta-analysis revealed that individuals with ASD are four-times more likely to have depression within their lifespan compared to those without ASD (Hudson, Hall, & Harkness, 2018). Another meta-analysis reported that approximately 40% have at least one comorbid anxiety disorder, including obsessive-compulsive disorder and social anxiety disorder (van Steensel, Bögels, & Perrin, 2011). High rates of depression and anxiety are associated with higher IQ in ASD, likely because higher functioning individuals have more insight into their difficulties and are more capable of communicating their distressed thoughts and feelings to warrant a diagnosis (Hudson et al., 2018; Sukhodolsky et al., 2008; van Steensel et al., 2011). ADHD symptoms occur in 40-83% of individuals with ASD, and shared genetic factors have been found (May et al., 2018; Naaijen et al., 2017; Pinto, Rijsdijk, Ronald, Asherson, & Kuntsi, 2016). Mediation analyses have shown that inattention and impulsivity in ADHD are linked to social communication deficits in ASD, while hyperactivity is linked to stereotyped, repetitive behaviours (Sokolova et al., 2017).

2.3.4. Genetic aetiology

Twin and family studies provide evidence for a genetic basis for ASD. A recent meta-analysis of 13 key twin studies in ASD showed higher correlations between monozygotic twins (.98) compared to dizygotic twins (.67) and heritability estimates of 64-91% (Tick, Bolton, Happé, Rutter, & Rijsdijk, 2016). Recurrence rates of 3-18% have been reported among younger siblings of children with ASD (Constantino, Zhang, Frazier, Abbacchi, & Law, 2010; Grønborg, Schendel, & Parner, 2013; Sandin et al., 2014), with a twofold increase for siblings from multiplex (i.e., more than one child with ASD) compared to simplex families (Ozonoff et

al., 2011). Recurrence risk is also higher in male versus female siblings, consistent with sex differences in the prevalence of ASD (Palmer, Beam, Agniel, & et al., 2017; Werling & Geschwind, 2015). Further, a "lesser variant" or broader phenotype of milder ASD-like features (i.e., Broader Autism Phenotype; see Section 2.4) is more prevalent in first- and second-degree relatives of individuals with ASD compared to the general population (Bolton et al., 1994; Pickles et al., 2000; Sucksmith et al., 2011).

The genetic aetiology of ASD is heterogeneous and complex, involving multiple genes, each a risk factor for the disorder (Ramaswami & Geschwind, 2018; Vorstman et al., 2017; Yin & Schaaf, 2017). As of September 2018, statistics from a database of all known genes associated with ASD (AutDB; Basu, Kollu, & Banerjee-Basu, 2009) have implicated over 1000 genes across approximately 1600 curated references. Researchers have used several approaches to uncover ASD-related genes, including linkage analyses (e.g., mapping genes to chromosomal regions by examining their transmission in families), genome-wide association studies (e.g., identifying variants across the entire genome that occur more frequently in people with the disease compared to controls), and whole-exome sequencing (e.g., identifying mutations in protein-encoding regions of the genome; Ramaswami & Geschwind, 2018; Yin & Schaaf, 2017).

Genetic findings in ASD include common and rare variants (i.e., allele frequency greater than or less than 5% of the general population, respectively), which have differing levels of penetrance (Ramaswami & Geschwind, 2018; Yin & Schaaf, 2017). Common variants include single nucleotide polymorphisms (SNPs; changes in a single base pair), which account for 40-60% of genetic liability in ASD and occur at higher rates in multiplex versus simplex families (Gaugler et al., 2014; Klei et al., 2012). Each common variant does not have a large enough

effect size to cause the disorder on its own, but has an additive effect when combined (Anney et al., 2012). Very large samples are therefore required to identify common risk loci (Devlin, Melhem, & Roeder, 2011).

Rare variants can be inherited from unaffected parents or occur *de novo* and generally pose a greater risk for ASD than common variants, although they do not necessarily have complete penetrance (Sebat et al., 2007; Stein, Parikshak, & Geschwind, 2013; Vorstman et al., 2017). Rare variants include pathogenic variants that cause monogenic syndromes associated with ASD, like Fragile X Syndrome (caused by mutations in *FMR1*), Rett syndrome (*MECP2*), tuberous sclerosis (*TSC1* and *TSC2*), and dup15q syndrome (Ramaswami & Geschwind, 2018). They also include copy number variants (CNVs; deletions or duplications of chromosomal regions), which when occurring *de novo*, are present in approximately 5-10% of ASD cases, with higher prevalence in simplex cases compared to multiplex families (Pinto et al., 2014; Sanders et al., 2015; Sebat et al., 2007). CNVs including specific genes (e.g., *NRXN1*, *CNTNAP2*, *NLGN4*, *SHANK2*, *SHANK1*) occur in both ASD and intellectual disability, accounting for high comorbidity between the conditions (Srivastava & Schwartz, 2014).

Common variants in genes and rare *de novo* CNVs in ASD have been implicated in a variety of mechanisms: synaptogenesis, cell proliferation, dendritic spine maturation, myelination, and neuronal migration and projection (Ben-David & Shifman, 2012; Bourgeron, 2015; Gai et al., 2011; Gilman et al., 2011). These genetic findings are consistent with some structural brain abnormalities reported in ASD. For example, post-mortem studies on ASD brain tissue have found increased glial cell numbers and decreased neurons in the prefrontal cortex and cerebellum (Edmonson, Ziats, & Rennert, 2014), among a wider range of neuropathological changes (Casanova et al., 2006; Courchesne, Mouton, Calhoun, & et al., 2011; Purcell, Jeon,

Zimmerman, Blue, & Pevsner, 2001). There is also consistent evidence for enlarged brain volume in ASD during early development (e.g., 2-4 years), followed by a marked decline in growth rates during adolescence and adulthood (Aylward, Minshew, Field, Sparks, & Singh, 2002; Courchesne, Campbell, & Solso, 2011; Courchesne et al., 2001; Schumann et al., 2010). Further, structural and functional hypoconnectivity between brain regions (e.g., frontal and posterior regions, corpus callosum, association fibre tracts) has been suggested to be a biomarker of ASD (Alexander et al., 2007; Geschwind & Levitt, 2007; Vissers, Cohen, & Geurts, 2012), although some studies also show patterns of hyperconnectivity or mixed hypo-and-hyperconnectivity (Di Martino et al., 2011; Monk et al., 2009; Supekar et al., 2013).

2.3.5. Environmental risk factors

Despite the high heritability of ASD, twin studies have shown that monozygotic pairs are not 100% concordant, suggesting some degree of nongenetic contribution to ASD or incomplete penetrance (Tick et al., 2016). Some twin studies have even reported that shared environmental factors account for as high as 55-78% of ASD risk (Frazier et al., 2014; Hallmayer, Cleveland, Torres, & et al., 2011), although most studies show minimal effects (Colvert et al., 2015; Ronald & Hoekstra, 2011; Sandin et al., 2017; Sandin et al., 2014). It is possible that early gene-environment interactions contribute to ASD risk in some individuals, where genotype may mediate outcome following exposure to specific environmental factors or vice versa, suggesting the role of epigenetic mechanisms (Lyall et al., 2017; Tordjman et al., 2014).

Several prenatal and neonatal risk factors have been identified, including advanced parental age, complications at birth (e.g., birth injury or trauma, umbilical-cord complications), maternal health during pregnancy (e.g., gestational diabetes, haemorrhage), multiple birth, low

birth weight, congenital malformations, anaemia, and hyperbilirubinemia (Gardener, Spiegelman, & Buka, 2011; Lyall et al., 2017). Exposure to bacterial and viral infections (e.g., rubella, influenza), teratogenic drugs (e.g., valproic acid, thalidomide), and antidepressants (e.g., selective serotonin reuptake inhibitors) *in utero* may also increase ASD risk (Christensen et al., 2013; Gidaya et al., 2014; Jiang et al., 2016). Other early risk factors include exposure to environmental chemicals like air pollution, heavy metals (e.g., mercury, lead), and pesticides, although little is known about the mechanisms by which they contribute to ASD (Dietert, Dietert, & DeWitt, 2011; Shelton, Hertz-Picciotto, & Pessah, 2012).

2.4. Broader Autism Phenotype

2.4.1. Defining the Broader Autism Phenotype

The Broader Autism Phenotype (BAP) is a set of behavioural and cognitive characteristics that resemble milder expressions of qualitatively similar traits of ASD (Bailey, Palferman, Heavey, & Le Couteur, 1998; Bolton et al., 1994; Sucksmith et al., 2011). Unlike ASD, the BAP is not a "disorder" or diagnostic entity, since it does not cause functional impairment which is severe enough to fall within the clinically significant range (Gerdts & Bernier, 2011). Figure 2.3 indicates where the BAP lies on the continuum of autistic traits across clinical and non-clinical cases. The BAP is present in 20-50% of parents and siblings of individuals with ASD, indicating a genetic liability for ASD (Bolton et al., 1994; Georgiades, Szatmari, Zwaigenbaum, & et al., 2013; Landa et al., 1992; Losh & Piven, 2007; Piven, Palmer, Landa, et al., 1997). Increased risk for the BAP is also reported in second-degree relatives, although its expression is milder than in first-degree relatives (Pickles et al., 2000; Piven, Palmer, Landa, et al., 1997). Further, higher rates of the BAP are found in multiplex rather than simplex families, suggesting that higher genetic loading for ASD is linked to higher genetic susceptibility for the BAP (Bernier, Gerdts, Munson, Dawson, & Estes, 2012; Constantino et

al., 2010; Gerdts, Bernier, Dawson, & Estes, 2013; Losh, Childress, Lam, & Piven, 2008; Szatmari et al., 2000; Virkud, Todd, Abbacchi, Zhang, & Constantino, 2009).

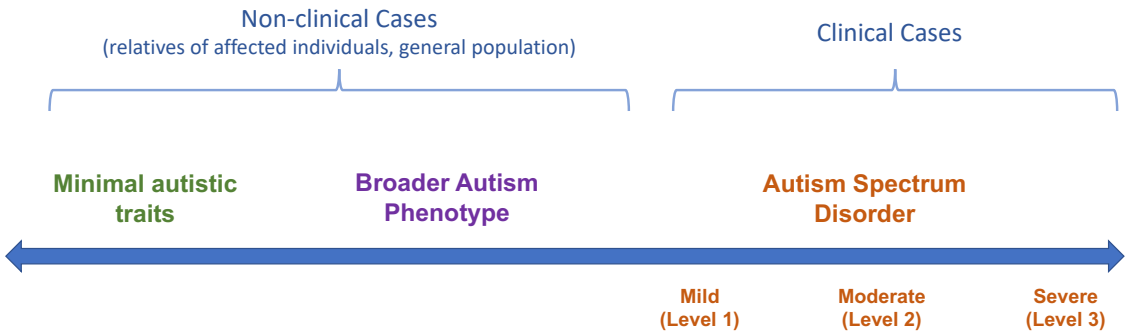


Figure 2.3. Continuum of autistic traits across non-clinical and clinical samples from low to high severity. Relatives of individuals with ASD and individuals from the general population may or may not demonstrate the BAP.

Early anecdotes of the BAP were documented by Kanner (1949), who observed that parents of children with ASD demonstrated a "mechanization of human relationships" (p. 421), where they would engage in solitary rather than social activities, be serious and formal in conversation, and show little warmth and affection towards their spouse and child. Kanner observed that parents were obsessive and rigid, adhering strictly to rules and expecting perfectionism from themselves and others. Asperger (1944) also acknowledged similar "autistic peculiarities" in parents, including social integration difficulties, abnormal expressive functions, and a "highly strung" personality. However, it was not until decades later that Folstein and Rutter (1977) provided the first empirical evidence of a genetic basis for the BAP. They reported that concordance rates between monozygotic and dizygotic twins climbed from 36 to 82% and 0 to 10%, respectively, when a broader phenotype encompassing cognitive deficits (e.g., language delay) and social/emotional difficulties was considered in co-twins without ASD. This led to the hypothesis that the BAP, and not ASD alone, can be transmitted in families with a genetic predisposition to ASD.

Unlike ASD, there is currently no gold-standard measure for defining BAP status, although several measures have been designed to identify components of the BAP in family members (Table 2.2). Bolton et al. (1994) performed the first systematic case-control family study on the BAP using the Family History Interview, which ascertains mild abnormalities in first- and second-degree relatives based on informant-report of their developmental history. Items were grouped into three domains of reciprocal social interaction (e.g., lack of affection, impaired social play, limited friendships, poor pragmatic language), communication deficits (e.g., language delay, reading/spelling difficulties), and repetitive or restricted behaviours/interests (e.g., circumscribed interests, rigid/perfectionistic style, repetitive behaviours), consistent with the DSM-IV classification criteria of ASD. Bolton et al. (1994) provided two working definitions for the BAP: (i) a "narrow definition", where a deficit in at least two of the three domains is required, and (ii) a "broad definition", where a deficit in any one of the three domains is sufficient. They found that 12.4% and 20.4% of siblings of children with ASD demonstrated the narrow and broad definitions, respectively, compared to only 1.6% and 3.2% of siblings of children with Down's Syndrome. Other studies using the Family History Interview have replicated findings of higher BAP prevalence in families with ASD compared to control families (Bolton, Pickles, Murphy, & Rutter, 1998; Fombonne, Bolton, Prior, Jordan, & Rutter, 1997; Murphy et al., 2000; Pickles et al., 2000; Piven, Palmer, Jacobi, Childress, & Arndt, 1997; Szatmari et al., 2000).

Consistent evidence for the BAP in families has also emerged from semi-structured interviews and questionnaires assessing personality traits. Several studies have reported that parents and siblings of children with ASD demonstrate higher rates of aloof (decreased interest in social interactions) and rigid (resistance to change) personality traits than controls, broadly consistent with the domains of social communication deficits and repetitive/restricted behaviour in ASD

(Hurley, Losh, Parlier, Reznick, & Piven, 2007; Losh et al., 2008; Murphy et al., 2000; Piven, Palmer, Landa, et al., 1997; Piven et al., 1994; Sasson, Lam, et al., 2013). A factor analysis of scores on the Modified Personality Assessment Schedule revealed three factors of personality traits in the BAP, specifically "withdrawn" (e.g., aloof, shy, undemonstrative), "tense" (e.g., anxious, rigid), and "difficult" (e.g., tactless, irritable), on which parents and siblings of children with ASD scored more than twice as high as Down Syndrome relatives (Murphy et al., 2000). Of note, relatives of individuals with ASD also have an increased risk for psychiatric disorders like depression, anxiety, obsessive-compulsive disorder, and social phobia, although these conditions are not consistently associated with scores on BAP measures and may therefore occur independently of the BAP (Bolton et al., 1998; Ingersoll & Hambrick, 2011; Micali, Chakrabarti, & Fombonne, 2004; Piven & Palmer, 1999; Wilcox, Tsuang, Schnurr, & Baida-Fragoso, 2003).

To assess pragmatic language difficulties in the BAP, Landa et al. (1992) developed the Pragmatic Rating Scale. This judges the appropriateness of conversational behaviour on a range of items, including disinhibited social communication (e.g., overly talkative, overly detailed, topic preoccupation), awkward/inadequate expression (e.g., inadequate clarification, vague, terse), and odd verbal interaction (e.g., inappropriate topics, little to-and-fro, overly familiar/informal). Landa et al. (1992) found that 42% of parents of affected individuals demonstrated some form of atypical pragmatic language compared to only 2% of control parents. Other studies have replicated communication difficulties on the Pragmatic Rating Scale for relatives of affected individuals (Ben-Yizhak et al., 2011; Folstein et al., 1999; Piven, Palmer, Landa, et al., 1997; Ruser et al., 2007), and some have shown higher self-ratings of pragmatic language difficulties on questionnaires assessing the BAP (Bishop et al., 2004; Hurley et al., 2007; Sasson, Lam, et al., 2013; Whitehouse, Barry, & Bishop, 2007).

Other social difficulties linked to the BAP in relatives include reduced number and quality of friendships (Bolton et al., 1994; Folstein et al., 1999; Losh & Piven, 2007) and reduced social cognition, which encompasses theory of mind, emotion recognition, face processing, and eye gaze (Adolphs, Spezio, Parlier, & Piven, 2008; Baron-Cohen & Hammer, 1997; Dorris, Espie, Knott, & Salt, 2004; Kadak, Demirel, Yavuz, & Demir, 2014; Losh, Adolphs, Poe, & et al., 2009; Losh & Piven, 2007; Oerlemans et al., 2014; Palermo, Pasqualetti, Barbati, Intelligente, & Rossini, 2006; Scheeren & Stauder, 2007; Tajmirriyahi et al., 2013; Wallace, Sebastian, Pellicano, Parr, & Bailey, 2010; Wilson, Freeman, Brock, Burton, & Palermo, 2010). A more detailed review of social cognition in ASD and the BAP is presented in Chapter 3. Executive functioning difficulties, weak central coherence or local processing bias, and poor structural language skills have also been reported in relatives, although their inclusion in the BAP remains questionable since findings are not consistent across studies (see the following for reviews: Gerdts & Bernier, 2011; Ingersoll & Wainer, 2014; Sucksmith et al., 2011).

Researchers have also used a number of self- and informant-report questionnaires (Table 2.2) to assess the BAP dimensionally, including the Autism Spectrum Quotient (AQ; Baron-Cohen et al., 2001), the Social Responsiveness Scale (SRS; Constantino, 2002), and the Broad Autism Phenotype Questionnaire (BAPQ; Hurley et al., 2007). Parents and siblings of individuals with ASD consistently show higher ratings on these questionnaires compared to controls (Bishop et al., 2004; Constantino et al., 2006; Hasegawa et al., 2015; Hurley et al., 2007; Sasson, Lam, et al., 2013; Wheelwright, Auyeung, Allison, & Baron-Cohen, 2010). A factor analysis of subscales from all three measures revealed three BAP dimensions reflecting aloofness, pragmatic language difficulties, and rigidity (Wainer, Ingersoll, & Hopwood, 2011). The BAPQ has been reported to have better psychometric properties (e.g., higher internal

consistency, criterion validity) than the AQ and SRS (Ingersoll, Hopwood, Wainer, & Brent Donnellan, 2011). The BAPQ also has a replicable structure corresponding to the three theoretical domains of the BAP, and hence, to DSM-IV criteria for ASD (Wainer et al., 2011). Of note, it was specifically designed to classify the BAP in relatives of individuals with ASD (Hurley et al., 2007), whereas the AQ and SRS were originally developed to identify individuals who meet a diagnosis for ASD (Baron-Cohen et al., 2001; Constantino, 2002). The BAPQ has normative cut-off values with high specificity and sensitivity to determine BAP-positive status (Hurley et al., 2007; Sasson, Lam, et al., 2013). It is therefore ideal for use with large samples where extensive clinical evaluation of the BAP is impractical (Sasson, Lam, et al., 2013). It is also ideal for screening control groups for the presence of BAP traits (Sasson, Lam, et al., 2013).

Overall, methods for classifying the BAP vary across studies, reflecting the absence of consensus criteria for defining its core features (Ingersoll & Wainer, 2014). Some studies have suggested that difficulties in a single ASD-related domain may be sufficient to indicate BAP status (Bolton et al., 1994; Losh et al., 2008; Piven, Palmer, Jacobi, et al., 1997; Sasson, Lam, et al., 2013), whereas others have suggested difficulties in at least two domains (Hurley et al., 2007). In support of the former approach, Sasson et al. (2013) showed that the majority of parents of children with ASD (21%) scored above cut-off on one of three subscales of the BAPQ, compared to only 9-13% and 1-4% who scored above cut-off on two and three dimensions, respectively. Using the Family History Interview, Bolton et al. (1994) reported similar percentages, with 20% of siblings demonstrating one domain of difficulty and 12% demonstrating two. Thus, it may be advisable to use less stringent criteria to classify BAP status and minimise the risk of excluding true positives. At best, it is imperative that researchers clearly state their criteria for assigning BAP status (e.g., specify the number of

domains required) to allow replication across studies. Future research could also examine how existing measures of the BAP correspond to more modern conceptualisations of ASD based on the DSM-5's two factor structure.

Table 2.2

Measures for Assessing the BAP in Family Members of Individuals with ASD

Measure	Reference	Description
Interview/Direct Observation		
Broader Phenotypes Autism Symptom Scale (BPASS)	Dawson et al. (2007)	- Semi-structured interview with parent about themselves and their child with ASD - Examiner rates BAP traits based on information provided on interview and direct observation - Quantitative measure of BAP traits in four domains: social motivation, social expressiveness, conversational skills, flexibility/range of interests
Family History Interview (FHI)	Bolton et al. (1994)	- Semi-structured interview with parent/other family member of individual with ASD - Examiner rates developmental history/ functioning of immediate and extended family members based on information provided - Categorical measure of BAP traits in three domains: social skills (including pragmatic language), communication (e.g., language/ reading delays), repetitive behaviours
Impressions of Interviewee (IoI)	Pickles et al. (2013)	- Observational rating scale used in conjunction with interview measures (e.g., FHI) - Examiner rates participants on 20 items corresponding to the BAP (e.g., facial expression, eye gaze, prosody, special topics in conversation) - Quantitative measure of BAP
Modified Personality Assessment Schedule-- Revised (M-PAS-R)	Piven et al., (1997); Piven et al., (1994)	- Semi-structured interview with the participant and separately with an informant

Measure	Reference	Description
		- Examiner rates personality based on information provided - Examines eight personality traits: conscientiousness, rigidity, aloofness, undemonstrativeness, anxiety, hypersensitivity to criticism, unresponsiveness, lack of tact (original version examines 18 traits)
Pragmatic Rating Scale (PRS)	Landa et al. (1992)	- Observational rating scale for participant's social use of language during conversation/ interaction with examiner - Three subscales: disinhibited social communication, awkward/inadequate expression, odd verbal interaction
Questionnaires		
Autism Spectrum Quotient (AQ)	Baron-Cohen et al. (2001)	- Self-report - Five subscales: social skills, communication, attention to detail, attention switching, imagination
Broad Autism Phenotype Questionnaire (BAPQ)	Hurley et al. (2007)	- Self- and informant-report versions - Three subscales: aloofness, pragmatic language difficulties, rigidity - Cut-off scores provided to determine BAP-positive status for the total score and each subscale
Children's Communication Checklist, Second Edition (CCC-2)	Bishop (2003)	- Parent-report - Assessed communication impairments more broadly (not specific to ASD) - Six subscales: language (speech, syntax, coherence), pragmatics, scripted language, context, nonverbal communication
Social Responsiveness Scale, First and Second Editions (SRS, SRS-2)	Constantino (2002); Constantino and Gruber (2012)	- Self-report (adults only) and informant-report (adults, children/adolescents) - Five subscales: social awareness, social cognition, social communication, social motivation, restricted/ repetitive behaviours - Total score indicates level of ASD severity (non-ASD, mild, moderate, severe)

Measure	Reference	Description
		- SRS-2 generates DSM-5 compatible scores for the two symptom domains

2.4.2. Endophenotypes of ASD

Specific traits of the BAP in relatives are candidates for endophenotypes of ASD (Abrahams & Geschwind, 2008; Ruparelia, Manji, Abubakar, & Newton, 2017; Viding & Blakemore, 2007). Endophenotypes are "intermediate phenotypes" that occur along the pathway between genes and the diagnostic state, and can be anatomical, electrophysiological, metabolic, or cognitive/behavioural in nature (Almasy & Blangero, 2001; Flint & Munafò, 2007; Gottesman & Gould, 2003). Figure 2.4 provides a schematic of the concept of the endophenotype in ASD. The study of endophenotypes has also been applied to other complex psychiatric and neurological disorders with polygenic causes like schizophrenia, ADHD, mood disorders, and Alzheimer's Disease (Allen, Griss, Folley, Hawkins, & Pearlson, 2009; Ertekin-Taner, 2011; Flint & Munafò, 2007; Hasler, Drevets, Manji, & Charney, 2004). According to criteria proposed by Gottesman and Gould (2003), endophenotypes must be: (i) heritable or influenced by genes, (ii) co-segregated or inherited together with the disorder in families, (iii) state-independent or present even when the disorder is not, and (iv) found at higher rates in family members without the disorder than in the general population.

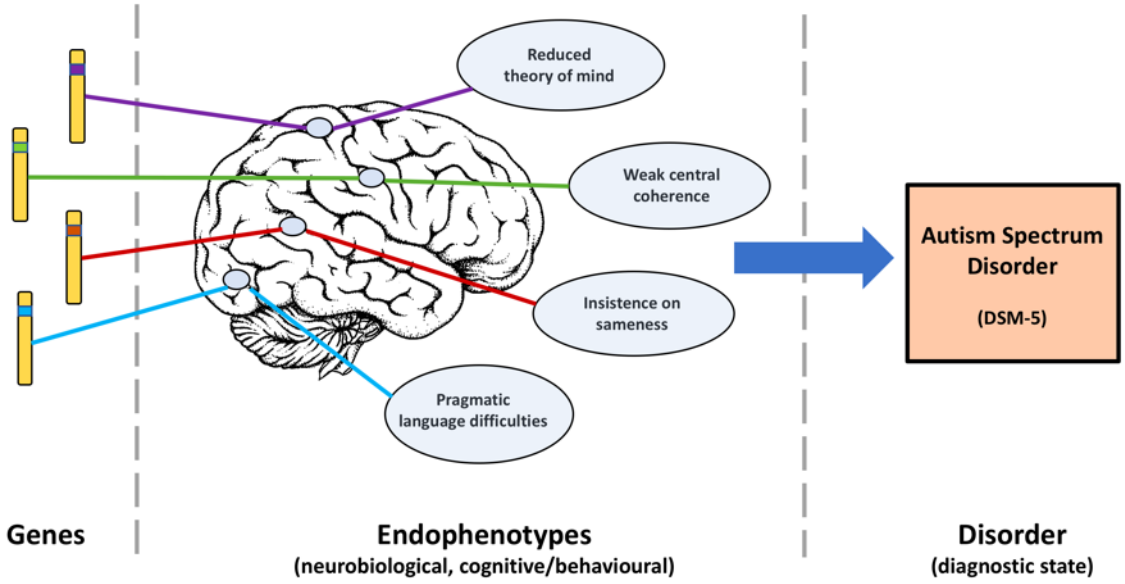


Figure 2.4. Schematic diagram of the concept of the endophenotype in ASD. Endophenotypes lie between the pathway of genes and the diagnostic state/disorder. Here, each gene influences a neurobiological component of ASD (e.g., abnormal brain structure/function; non-specific regions pictured here), which is associated with a specific symptom of ASD. Together, these neurobiological and cognitive/behavioural endophenotypes (along with others not represented here) contribute to the full syndrome or diagnostic state of ASD. In reality, any given endophenotype may have a polygenic rather than monogenic cause, although its genetic composition is still expected to be less complicated than that of the full diagnostic state (Walters & Owen, 2007).

Endophenotypes offer an advantage for research on the aetiology of complex polygenic disorders. Since endophenotypes represent quantifiable components of a disorder, they are also likely to be associated with fewer genes and fewer biological pathways than the disorder itself (Almasy & Blangero, 2001; Gottesman & Gould, 2003). In principle, identifying genes based on the presence of endophenotypes should therefore be less complicated than gene discovery based on diagnostic state alone. For example, researchers can use specific endophenotypes as the primary inclusion/exclusion criteria to create more homogeneous subgroups for genetic research (Gottesman & Gould, 2003; Walters & Owen, 2007). Researchers can also use endophenotypes to identify larger samples of individuals who potentially carry susceptibility genes (e.g., both affected individuals and family members who

do not meet diagnostic criteria), which will improve statistical power for detecting genes of small effect size (Almasy & Blangero, 2001; Flint & Munafò, 2007; Walters & Owen, 2007).

Quantitative trait loci for ASD have been successfully identified in multiplex families based on linkage to endophenotypes for language delay (Alarcón, Yonan, Gilliam, Cantor, & Geschwind, 2005; Bradford et al., 2001; Buxbaum et al., 2001; Shao et al., 2002; Spence et al., 2006), social responsiveness (Coon et al., 2010; Duvall et al., 2007; Lowe, Werling, Constantino, Cantor, & Geschwind, 2015), savant skills (Nurmi et al., 2003), and repetitive behaviour (Cannon et al., 2010; Shao et al., 2003). Table 2.3 lists the chromosomes on which these quantitative trait loci have been found. Importantly, linkage analyses have also shown that classifying family members with behavioural endophenotypes of ASD as "affected" can further strengthen the signal at various loci, representing an advantage of including the BAP to improve the power of genetic analyses (Bradford et al., 2001; Piven et al., 2013; Woodbury-Smith et al., 2015).

Table 2.3

Chromosomes Linked to Endophenotypes in ASD

Endophenotype	Chromosome	References
Language delay	2, 3, 7, 17	Alarcón et al. (2005), Buxbaum et al. (2001), Shao et al. (2002), Spence et al. (2006)
Social responsiveness	4, 7, 8, 9, 10, 11, 13, 15, 17, 19	Coon et al. (2010), Duvall et al. (2007), Lowe et al. (2015)
Repetitive behaviours	2, 15	Cannon et al. (2010), Shao et al. (2003)
Savant skills	15	Nurmi et al. (2003)

Less research has been conducted to link genetic loci to endophenotypes related to brain structure and function in ASD (e.g., Rudie et al., 2012; Scott-Van Zeeland et al., 2010), despite such studies providing valuable insights into the relationship between genes, brain, and behaviour in ASD. Neurobiological endophenotypes are useful for studying more direct effects of genetic variants on brain function in ASD (Cannon & Keller, 2006; Glahn, Thompson, & Blangero, 2007; Meyer-Lindenberg & Weinberger, 2006). Neurobiological endophenotypes are also more sensitive to group differences (e.g., ASD or BAP versus typically-developing controls), and may be expressed in carriers of susceptibility genes who do not demonstrate behavioural endophenotypes on testing (Hariri & Weinberger, 2003; Meyer-Lindenberg & Weinberger, 2006).

Measures conducive to the identification of neurobiological endophenotypes include those that reliably elicit activation in functional brain networks implicated in the disorder (Hariri & Weinberger, 2003; Meyer-Lindenberg & Weinberger, 2006). Several functional MRI (fMRI) studies have consistently revealed atypical brain function in ASD on tasks assessing social cognition, neuropsychological functions, language and communication, and sensory and motor processing (Lombardo, Baron-Cohen, Belmonte, & Chakrabarti, 2011; Philip et al., 2012). A smaller body of fMRI research has shown similar patterns of atypical brain activation in parents and siblings of individuals with ASD, even in the absence of behavioural traits (Baron-Cohen, Ring, et al., 2006; Billeci et al., 2016; Holt et al., 2014; Kaiser et al., 2010; Spencer et al., 2011; Wilson et al., 2013; Yucel et al., 2015). Similarities in neural correlates between probands and their relatives suggest the presence of neurobiological BAP markers, which potentially qualify as robust endophenotypes for gene-brain mapping in ASD (Billeci et al., 2016). Neurobiological markers of ASD and the BAP are reviewed more extensively in Chapter 3, in relation to abnormal functioning of the "social brain".

2.4.3. Expression in the general population

The BAP is not confined to families of individuals with ASD but extends to the general population (Ingersoll & Wainer, 2014; Sucksmith et al., 2011). BAP traits in the general population are typically measured using questionnaires (Ingersoll et al., 2011; Ingersoll & Wainer, 2014), most commonly the AQ (Ruzich et al., 2015). AQ scores are normally distributed in the general population (Hurst, Mitchell, Kimbrel, Kwapil, & Nelson-Gray, 2007; Ruzich et al., 2015), as are scores on the SRS (Constantino & Todd, 2003; Constantino & Todd, 2005) and the BAPQ (Ingersoll et al., 2011; Sasson, Lam, et al., 2013). Studies utilising samples of university undergraduate students have reported that approximately 18-40% meet categorical criteria for the BAP, based on cut-off values for the total score on the BAPQ (Sasson, Nowlin, & Pinkham, 2013; Wainer, Block, Donnellan, & Ingersoll, 2013). Another study showed that approximately 5-9% of parents of typically-developing children meet cut-off values on the BAPQ, compared to a higher percentage of 14-23% of parents of children with ASD (Sasson, Lam, et al., 2013).

BAP traits have also been shown to be heritable in the general population (Constantino & Todd, 2003; Constantino & Todd, 2005; Hoekstra, Bartels, Verweij, & Boomsma, 2007; Lundström, Chang, Råstam, & et al., 2012; Robinson, Koenen, McCormick, & et al., 2011). One study found that AQ scores correlated at .55 for monozygotic twin pairs, .37 for dizygotic pairs, and .32 for first-degree relative pairs from the general population, with 57% of variance in twins and their siblings accounted for by additive genetic effects (Hoekstra et al., 2007). Participants in the study were not screened for ASD. There is some evidence to suggest that BAP traits in the general population are influenced by similar susceptibility genes to those that influence ASD in the clinical population (Jones et al., 2014; Pourcain et al., 2013), although such research is scarce. Accordingly, studying the BAP in the general population may inform research on

the genetic aetiology of ASD by allowing the recruitment of larger sample sizes for linkage analyses (Constantino & Todd, 2003).

Responses on BAP questionnaires correlate with measures of social functioning, personality, psychopathy, and cognition in the general population (Ingersoll & Wainer, 2014). For example, higher scores on BAP questionnaires correlate with increased loneliness and lower quality of friendships or relationship satisfaction (Faso, Corretti, Ackerman, & Sasson, 2016; Jamil, Gragg, & DePape, 2017; Jobe & Williams White, 2007; Pollmann, Finkenauer, & Begeer, 2010; Wainer et al., 2013). Higher scores on BAP questionnaires also correlate with higher levels of neuroticism and lower levels of extraversion and agreeableness (Austin, 2005; Wakabayashi, Baron-Cohen, & Wheelwright, 2006), as well as higher rates of schizotypy, social phobia, obsessive-compulsive disorder, and depression (Kunihira, Senju, Dairoku, Wakabayashi, & Hasegawa, 2006; Wainer et al., 2011). Moreover, associations between the BAP and reduced social cognition (e.g., theory of mind, empathy, emotion recognition) have been established (Ingersoll, 2010; Miu, Pană, & Avram, 2012; Sasson, Nowlin, et al., 2013), as discussed in more detail in Chapter 3. As with research on the BAP in families, associations between the BAP in the general population and other domains of cognition (e.g., weak central coherence, executive functioning) have yielded inconsistent findings (see Ingersoll & Wainer, 2014).

2.5. Chapter Summary

Under current DSM-5 criteria, the broad diagnostic category of ASD is characterised by two core domains of impairment in social communication and restricted repetitive behaviours/interests. Heterogeneity of clinical presentation (e.g., constellation and severity of symptoms, intellectual ability, language development, comorbidities) is common among

individuals with ASD. The genetic aetiology of ASD is also heterogeneous and complex, involving multiple gene variants with differing levels of penetrance. Milder, subclinical ASD-like traits known as the BAP are more prevalent in relatives of individuals with ASD compared to the general population, supporting a genetic basis for the disorder. BAP traits in relatives represent endophenotypes of ASD, which are presumed to be associated with fewer genes than the full diagnostic state and may consequently facilitate gene discovery in ASD.

Following the broad overview of ASD and the BAP presented here, the next chapter reviews evidence for reduced social cognition and abnormal functioning of the "social brain" in ASD and the BAP. Social cognitive deficits—particularly related to theory of mind, empathising, and the processing of faces—are among the most widely documented symptoms of impaired social communication in ASD. Research on emotional voice processing in ASD and the BAP, which constitutes a less explored aspect of social cognition and the basis for this thesis, will be presented in a separate chapter (Chapter 4).

CHAPTER 3

Social Cognition and the Social Brain

Overview: This chapter provides an overview of social cognitive deficits commonly reported in ASD, particularly related to theory of mind, empathy, and face processing. Atypical brain function underlying these processes is discussed. This chapter also reviews studies showing similar behavioural and neurobiological profiles within the BAP in family members of individuals with ASD and the general population, providing evidence for potential endophenotypes of social cognition in ASD.

3.1. Social Cognition and the Social Brain

Social cognition broadly refers to our ability to process socially relevant information, which consequently guides how we interact with others (Beer & Ochsner, 2006; Happé et al., 2017). Perception of the self and other is crucial for social cognition, particularly with regards to how both are alike or different (Beer & Ochsner, 2006; Decety & Sommerville, 2003). For example, one might consciously or unconsciously draw on one's own experience in a similar situation to infer the thoughts and feelings of others. Importantly, one must also recognise that others have a set of experiences distinct from one's own, which influence their social behaviour and perceptions.

Components of social cognition include affiliation and social motivation, action representation (e.g., biological motion perception, action recognition, imitation), social attention, social learning, theory of mind (ToM), empathy, and emotion recognition (see Happé et al., 2017 for a review). Although these components have distinct features, they are not mutually exclusive and may share common processes (Gallese, Keysers, & Rizzolatti, 2004; Happé et al., 2017). This chapter focuses on ToM, empathy, and emotion recognition for facial expressions (plus face processing more broadly) in ASD and the BAP, since these components are hypothesised to underlie social communication deficits in ASD and are pertinent to our discussion of emotional voice processing in the following chapter.

Social cognition is mediated by the "social brain", a widely distributed network of regions that are implicated in the processing of social information (Brothers, 1990; Frith, 2007; Gotts et al., 2012; Pelphrey, Shultz, Hudac, & Vander Wyk, 2011). Brothers (1990) first conceptualised this network based on single-cell recordings in monkeys performing a variety of social behaviours. They proposed that the amygdala, superior temporal sulcus (STS), fusiform gyrus

and orbitofrontal cortex (OFC) are major components within this network. Since then, researchers have suggested additional regions, including the medial prefrontal cortex (mPFC), inferior frontal gyrus (IFG), anterior cingulate cortex (ACC), temporoparietal junction (TPJ), intraparietal sulcus, anterior insula, and the striatum, among others (Adolphs, 1999; Amodio & Frith, 2006; Bhanji & Delgado, 2014; Gotts et al., 2012; Mar, 2011; Rizzolatti & Craighero, 2004; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). Here, sub-networks of the social brain underlying ToM, empathy, and face processing are discussed in relation to their atypical function in ASD and the BAP.

3.2. Theory of Mind

3.2.1. Impaired theory of mind

The impaired theory of mind (ToM) or "mind blindness" hypothesis is one of the most influential cognitive theories of ASD, accounting primarily for the social communication domain of impairment (Baron-Cohen, 2000). ToM, also known as mentalising or mindreading, refers to an individual's ability to take the perspectives of others and understand how their mental states (e.g., beliefs, intentions, desires) influence their behaviour (Baron-Cohen, Leslie, & Frith, 1985; Premack & Woodruff, 1978). ToM emerges in early childhood, with evidence that typically-developing children are able to pass first-order false belief tasks by 4-5 years (Hogrefe, Wimmer, & Perner, 1986; Wimmer & Perner, 1983). A popular example is the "Sally-Anne" task (Baron-Cohen et al., 1985), which involves inferring the mental state of one character from a story enacted with dolls. In the story, Sally puts a marble in her basket then leaves the room, and in her absence, Anne transfers the marble from the basket to a box. Participants are then asked where Sally will look for her marble when she returns to the room. If participants indicate the basket (instead of the box), they then demonstrate that they can take one other person's perspective and distinguish it from their own knowledge about the situation.

Typically-developing children are able to pass more complex, second-order false-belief tasks by 6-7 years (Astington, Pelletier, & Homer, 2002; Perner & Wimmer, 1985). These tasks require participants to consider what one character believes about the perspective of another character. For example in the "John and Mary" task (Perner & Wimmer, 1985), two characters see an ice cream truck in the park and the ice cream man tells them independently (without each other's knowledge) that he will be leaving to sell ice cream at the church. Participants are then asked where John thinks Mary will go to look for ice cream. If participants indicate the park (instead of the church), then they demonstrate that they can understand "embedded" attributions of mental states held by multiple individuals (e.g., "John *thinks* that Mary *thinks* that…").

Impaired ToM in ASD was first assessed by Baron-Cohen et al. (1985), who showed that 80% of children with ASD (M_{age} = 11 years) failed the Sally-Anne task, while only 14% of children with Down Syndrome (M_{age} = 10 years) and 23% of typically-developing children (M_{age} = 4 years) failed the task. The authors reasoned that low intellectual functioning was unlikely to fully account for poor task performance in the ASD group (mean verbal and nonverbal mental age of 5 and 9 years, respectively), since the Down Syndrome group performed well despite having more severe intellectual impairment. Of note, the minority of children with ASD who passed the first-order task failed on the second-order John and Mary task, demonstrating a developmental delay of ToM (Baron-Cohen, 1989).

Poor performance on first- and second-order false-belief tasks was replicated in subsequent studies, providing support for the ToM account of ASD (Happé, 1995; Leslie & Frith, 1988; Ozonoff, Pennington, & Rogers, 1991; Perner, Frith, Leslie, & Leekam, 1989; Yirmiya, Erel,

Shaked, & Solomonica-Levi, 1998). Individuals with HFA/AS tend to perform as well as controls on these tasks, however, indicating a link between verbal IQ and task performance (Bowler, 1992; Dahlgren & Trillingsgaard, 1996; Happé, 1995). It is possible that higher-functioning individuals depend on verbal mediation or understanding of linguistic constructs (e.g., syntax, semantics) to logically reason through false-belief scenarios (Bowler, 1992; Happé, 1995; Tager-Flusberg & Joseph, 2005).

Individuals with HFA/AS who pass second-order false-belief tasks generally perform worse than healthy controls on "advanced ToM" tasks, like the Strange Stories Task (Brent, Rios, Happé, & Charman, 2004; Happé, 1994; Jolliffe & Baron-Cohen, 1999; Kaland, Callesen, Møller-Nielsen, Mortensen, & Smith, 2008). The Strange Stories Task (Happé, 1994) includes everyday scenarios in which a character says something they do not mean literally (e.g., sarcasm, irony, joke, double bluff, white lie). Participants then identify whether what was said is true and discern the character's reason for saying it. Individuals with ASD tend to take the statements literally or misinterpret them, thereby failing to provide context-appropriate responses about the mental states of others (Happé, 1994; Jolliffe & Baron-Cohen, 1999). In one example, individuals with ASD misinterpreted a sarcastic statement (i.e., "Oh yes, it's a lovely day for a picnic") that Sarah said to Tom in the rain as something she said just to cheer him up (Jolliffe & Baron-Cohen, 1999). In another example, a white lie that Helen told when her parents gave her presents she did not like (i.e., "It's lovely, thank you. It's just what I wanted") was misinterpreted as a joke (Happé, 1994).

Individuals with HFA/AS also show deficits on the Faux Pas Task, another test of advanced ToM (Baron-Cohen, O'riordan, Stone, Jones, & Plaisted, 1999; Spek, Scholte, & Van Berckelaer-Onnes, 2010; Zalla, Sav, Stopin, Ahade, & Leboyer, 2009). The task includes

social scenarios in which a character accidentally blurts out a faux pas (i.e., social blunder committed without malice), which may offend others in the story. For example, James breaks Richard's toy plane, to which Richard responds, "Don't worry I never really liked it anyway—someone gave it to me for my birthday," without realising that the present was from James. Participants are required to: 1) identify the faux pas, 2) evaluate the character's intention for committing it, and 3) judge its emotional impact on others. Zalla et al. (2009) discovered that adults with AS were able to successfully identify the faux pas, but failed to discern the character's intentions (e.g., "It was an honest mistake") and instead, accused him/her of having malicious intent (e.g., "He said it deliberately to offend him" or "He was jealous"). The authors also found that adults with AS over-detected faux pas situations in control stories where no social blunder was committed. These findings are consistent with performance on moral reasoning tasks, on which adults with HFA assign more blame and punishment to characters who accidentally cause harm to others (Buon et al., 2013; Moran et al., 2011). These attributions support reduced ToM in ASD, where affected individuals have difficulty judging the intentions of others based on outcome (Buon et al., 2013; Moran et al., 2011).

ToM deficits in HFA/AS also emerge on the Reading the Mind in the Eyes Task (Eyes Task), which assesses the judgment of complex mental states from expressions in the eye-region alone (Baron-Cohen, Wheelwright, Jolliffe, & Therese, 1997; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Brent et al., 2004; Kaland et al., 2008; Kleinman, Marciano, & Ault, 2001). These complex mental states, also referred to as "complex emotions", correspond to labels like *playful*, *serious*, *fantasising*, *sceptical*, *preoccupied*, *accusing*, *hateful*, and *concerned* (Baron-Cohen et al., 2001). Poor performance on the Eyes Task is associated with higher scores on the AQ for individuals with HFA/AS and healthy controls alike (Baron-Cohen et al., 2001). However, performance on the Eyes Task does not correlate with performance on

other advanced ToM tasks like the Strange Stories Task, indicating that it assesses different conceptual skills (Brent et al., 2004; Kaland et al., 2008; Roeyers, Buysse, Ponnet, & Pichal, 2001). For example, while most ToM tasks assess internal, unobservable entities within a given social context (engaging top-down processes), the Eyes Task assesses mental state information from observable features presented without contextual information (engaging botton-up processes; Baron-Cohen et al., 1997). Some researchers have argued that the Eyes Task is a more appropriate measure of emotion recognition than ToM ability, since it does not require the attribution of beliefs, it assesses attitudes rather than content (e.g., she's contented about something, but what?), and it relates closely to alexithymia or the poor recognition of one's own emotions (Jarrold, Butler, Cottington, & Jimenez, 2000; Oakley, Brewer, Bird, & Catmur, 2016). Despite this, the Eyes Task continues to be used across studies of ToM and emotion recognition and appears to have merits for both.

Researchers have adapted the Eyes Task to test complex mental states in the auditory domain ("Reading the Mind in the Voice" task; Golan, Baron-Cohen, Hill, & Rutherford, 2007; Rutherford, Baron-Cohen, & Wheelwright, 2002) and across multiple sensory modalities ("Reading the Mind in Films" task; Golan, Baron-Cohen, Hill, & Golan, 2006). The Reading the Mind in the Voice Task requires participants to infer complex mental states from paralinguistic information (i.e., prosody/tone of voice) embedded in short voice-recorded spoken phrases (e.g., "No I honestly do.", "What a pair!"). The Reading the Mind in Films Task requires participants to integrate visual, auditory, and contextual information from short movie clips of social scenes to infer the actor's mental state. Individuals with HFA/AS demonstrate low performances on both tasks, suggesting that ToM deficits extend beyond the visual domain (Golan, Baron-Cohen, & Golan, 2008; Golan, Baron-Cohen, Hill, et al., 2006; Golan et al., 2007; Rutherford et al., 2002). Like the Eyes Task, these two tasks have also been

used interchangeably to assess mental state attributions and emotion recognition (Golan et al., 2008; Golan et al., 2007), although their relationship with measures of alexithymia have yet to be examined.

3.2.2. Theory of mind network

Several neuroimaging studies have been conducted to identify brain regions underlying ToM in the general population (Carrington & Bailey, 2009; Mahy, Moses, & Pfeifer, 2014; Mar, 2011; Schurz et al., 2014). Findings are heterogeneous, with different regions reported across studies depending on the type of task and stimuli used (Mar, 2011; Schurz et al., 2014). Thus, some researchers have proposed that ToM-related brain areas can be better mapped according to specific tasks that tap into different components of ToM, like understanding false beliefs, inferring mental states from the eyes, or story-based versus non-verbal tasks (Schaafsma, Pfaff, Spunt, & Adolphs, 2015; Schurz & Perner, 2015; Schurz et al., 2014). Despite the heterogeneity, meta-analyses and systematic reviews have revealed several regions of overlap between different ToM tasks, supporting a core network for inferring the mental states of others (Bzdok et al., 2012; Carrington & Bailey, 2009; Schurz et al., 2014). This includes the mPFC, OFC, TPJ, and STS (Bzdok et al., 2012; Carrington & Bailey, 2009; Mar, 2011; Schurz et al., 2014), as displayed in Figure 3.1. Other ToM regions implicated in meta-analyses include the middle temporal gyrus (MTG), IFG, posterior cingulate cortex (PCC), precuneus, and temporal poles (Bzdok et al., 2012; Mar, 2011; Schurz et al., 2014).

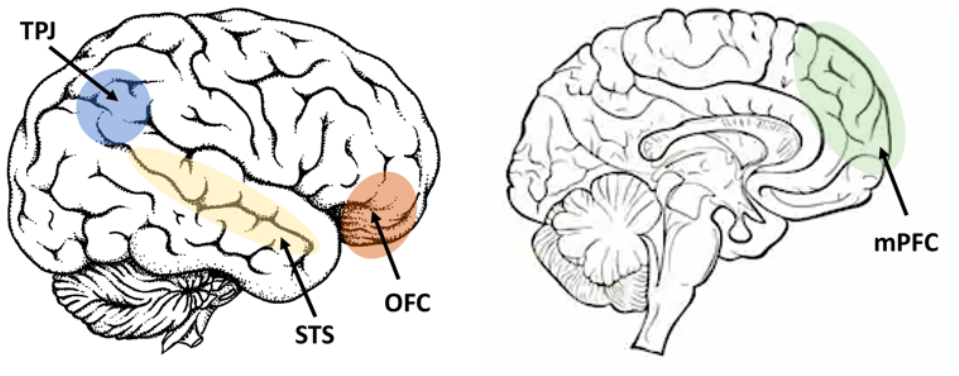


Figure 3.1. Core ToM network. TPJ = temporoparietal junction; STS = superior temporal sulcus; OFC = orbitofrontal cortex; mPFC = medial prefrontal cortex.

Studies assessing the neural correlates of impaired ToM in ASD generally show hypoactivation in the core ToM network and other regions for mentalising (Philip et al., 2012). Happé et al. (1996) conducted the first neuroimaging study of ToM in ASD using positron emission tomography (PET). They found that adults with AS scored lower than controls on ToM story comprehension and unlike controls, did not show activation in the left dorsal mPFC. Another PET study, which used a similar story-based task, revealed that both control and AS groups demonstrated activation in the bilateral mPFC, although activation in the AS group was significantly reduced (Nieminen-von Wendt et al., 2003). Hypoactivation of the mPFC (plus STS and temporal poles) was also reported in a PET study using a non-verbal ToM task, where participants attributed mental states to animations of geometric shapes (Castelli, Frith, Happé, & Frith, 2002).

Individuals with ASD demonstrate reduced specialisation of the right TPJ for ToM (Kana, Libero, Hu, Deshpande, & Colburn, 2014; Lombardo, Chakrabarti, Bullmore, & Baron-Cohen, 2011; Mason, Williams, Kana, Minshew, & Just, 2008). For example, Lombardo and colleagues (2011) found that controls activated the right TPJ only when making mental state judgments about the self and others (e.g., how likely are you/the Queen to think that keeping a

diary is important?), whereas the ASD group activated this region when making both mental state and physical judgments (e.g., how likely are you/the Queen to have bony elbows?). Mason and colleagues (2008) reported that controls showed higher right TPJ activation when making judgments about passages on intentionality compared to passages on physical causality or emotional states. In contrast, the ASD group demonstrated no significant difference in right TPJ activation across all three passages.

Baron-Cohen, Ring, et al. (1999) assessed the neural correlates of ToM in individuals with HFA/AS using an fMRI paradigm of the Eyes Task. The HFA/AS group was worse than controls at inferring mental states in the eyes. They also demonstrated less extensive activation than controls in frontal ToM regions (e.g., mPFC, IFG) and no activation in the amygdala. Although the amygdala is not consistently implicated in ToM (e.g., Carrington & Bailey, 2009; Mar, 2011), hypoactivation of this region on the Eyes Task may reflect concurrent difficulties with emotional processing in ASD (Baron-Cohen, Ring, et al., 1999). Another fMRI study using the Eyes Task reported hypoactivation in the IFG, OFC, MTG, and temporal poles for individuals with ASD compared to controls, with neither group demonstrating activation in the amygdala (Holt et al., 2014).

Underconnectivity in the ToM network has been reported in ASD. One study reported reduced functional connectivity between frontal (e.g., mPFC, OFC) and posterior (e.g., TPJ, STS, MTG) regions of the ToM network when individuals with ASD attributed mental states to geometric animations (Kana, Keller, Cherkassky, Minshew, & Just, 2009). Another study reported reduced functional connectivity between the TPJ and premotor regions implicated in the mirror neuron system (MNS; see Section 3.3.2), suggesting disruptions to the role of simulation in mentalising (Kana et al., 2014). Reduced resting-state connectivity has been

reported between the ToM network and regions associated with emotional face processing and the sense of self (Cheng, Rolls, Gu, Zhang, & Feng, 2015). Further, studies using diffusion tensor imaging (DTI) have revealed white matter abnormalities (e.g., reduced fractional anisotropy) within the ToM network (Barnea-Goraly et al., 2004; Kana et al., 2014).

3.2.3. Expression in the BAP

There is mixed evidence for reduced ToM in the BAP. Studies have shown that parents and siblings of children with ASD perform more poorly than controls on false belief tasks and other story-based measures of ToM (Eyuboglu, Baykara, & Eyuboglu, 2018; Gliga, Senju, Pettinato, Charman, & Johnson, 2014; Gokcen, Bora, Erermis, Kesikci, & Aydin, 2009; Tsang, Gillespie-Lynch, & Hutman, 2016). In contrast, other studies have shown that siblings of affected children demonstrate intact performance on similar measures, although the null effect could have been influenced by small sample size (Ozonoff, Rogers, Farnham, & Pennington, 1993; Shaked, Gamliel, & Yirmiya, 2006).

Parents and siblings of individuals with ASD demonstrate difficulties on the Eyes Task (Baron-Cohen & Hammer, 1997; Dorris et al., 2004), although poor performance by relatives is not consistent across studies (Gokcen et al., 2009; Tajmirriyahi et al., 2013). Some studies have reported reduced performance on the Eyes Task only for parents with aloof BAP traits, but not for non-aloof parents (Losh et al., 2009; Losh & Piven, 2007). Among aloof parents, lower performance on the Eyes Task correlated with lower quality of friendships and pragmatic language difficulties (Losh & Piven, 2007). One study also reported poorer performance on the "Reading the Mind in the Voice" task in parents, suggesting reduced auditory-related ToM in the BAP (Tajmirriyahi et al., 2013).

fMRI studies have shown that relatives of individuals with ASD demonstrate reduced activation in ToM regions when inferring mental states on the Eyes Task (Baron-Cohen, Ring, et al., 2006; Holt et al., 2014). Baron-Cohen, Ring, et al. (2006) reported that parents had lower activation in the MTG and IFG relative to controls. Holt et al. (2014) reported that female siblings demonstrated less activation in the MTG and mPFC (plus visual areas) compared to female controls, while no significant group differences were reported for males. Of note, these regions of reduced activation are similar to those implicated on the Eyes Task in individuals with ASD (Baron-Cohen, Ring, et al., 1999; Holt et al., 2014), suggesting potential neurobiological endophenotypes for mentalising in ASD. One DTI study also reported that children with ASD and their siblings showed white matter abnormalities (e.g., reduced fractional anisotropy) in similar ToM regions, including the mPFC, superior temporal gyrus (STG), PCC, and TPJ (Barnea-Goraly, Lotspeich, & Reiss, 2010).

Behavioural studies have assessed the relationship between ToM and self-ratings of BAP traits within the general population. One study reported that slower reaction time on the Eyes Task correlated with higher self-ratings of BAP traits (i.e., high AQ scores) in a sample of undergraduate students (Miu et al., 2012). Another study on undergraduate students reported no correlation between self-ratings of BAP traits (i.e., high BAPQ scores) and performance on a ToM task which measured the attribution of intentions (Sasson, Nowlin, et al., 2013). However, the authors reported that students with "social BAP-positive" status (i.e., those who met categorical cut-off scores for aloof personality and pragmatic language difficulties on the BAPQ) demonstrated a trend for lower social cognition scores (i.e., composite score on ToM and face processing tasks) compared to students with "social BAP-negative" status. Overall, these findings suggest that reduced ToM abilities may extend to the BAP in the general population.

3.3. Empathising

The "Empathising-Systemising" hypothesis is a wholistic cognitive theory of ASD, which accounts for both domains of impairment in social communication and restricted, repetitive behaviours (Baron-Cohen, 2009). It suggests that individuals with ASD demonstrate weaknesses in empathising but strengths in systemising. Empathising refers to the drive to understand and respond to the thoughts and emotions of others, while systemising refers to the drive to understand systems (Baron-Cohen, 2009). Here, a "system" refers to "something that takes inputs, which can then be operated on in *variable* ways, to deliver *different* outputs in a rule-governed way" (Baron-Cohen, Richler, Bisarya, Gurunathan, & Wheelwright, 2003, p. 361). One can predict the behaviour of a system by drawing "if-then" associations between the operation and output (e.g., "*x* always causes *y*", or "if I do *x*, then *y* should happen"), provided that the evidence is precise and consistent. Empathising relates to social phenomena that are highly flexible and open to multiple interpretations across contexts, whereas systemising relates to phenomena that follow a constant pattern, are highly predictable, and ultimately fact-based (e.g., laws of nature, language syntax, mathematical formulae, workings of a machine; Baron-Cohen, 2009; Baron-Cohen et al., 2003). In this section, only the concept of empathising and its neural correlates in ASD are reviewed, since it is more pertinent to the discussion on social cognition. A brief overview of systemising in ASD is presented as supplementary material in Appendix B.

3.3.1. Reduced empathising

Empathy is a multidimensional construct defined by cognitive and affective factors (Baron-Cohen, 2009; Davis, 1983; Decety & Jackson, 2004; Decety & Meyer, 2008; Preston & de Waal, 2002; Smith, 2006). Cognitive empathy (synonymous to ToM) refers to one's ability to

understand the mental and emotional states of others, and relies on the higher-order, top-down processing of social information (Decety & Jackson, 2004; Preston & de Waal, 2002). In contrast, affective empathy refers to one's ability to "catch" or experience and express the emotions of others (i.e., "emotional contagion"), and to elicit an appropriate emotional response (i.e., "empathic concern") to their distress (Decety & Jackson, 2004; Hatfield, Cacioppo, & Rapson, 1992). Affective empathy—particularly relating to emotional contagion—can occur at a basic, physiological level outside of one's conscious awareness (Hatfield et al., 1992; Preston & de Waal, 2002). For example, researchers have proposed that individuals tend to spontaneously mimic the emotional facial/vocal/postural expressions of others, which may subsequently influence their own experience and recognition of the other person's affective state through afferent feedback mechanisms (Decety & Meyer, 2008; Hatfield, Bensmana, Thorntona, & Rapsona, 2014; Hatfield, Cacioppo, & Rapson, 1994; Prochazkova & Kret, 2017).

Reduced emotional contagion in ASD has been inferred from facial mimicry paradigms. Compared to controls, high-risk infants and children with ASD have been observed to smile less in response to their mothers' smiles (Dawson, Hill, Spencer, Galpert, & Watson, 1990) and to demonstrate less valence-congruent facial expressions to positive and negative expressions displayed by experimenters (Scambler, Hepburn, Rutherford, Wehner, & Rogers, 2007). Studies using electromyography (EMG) and direct observation have shown that adolescents and adults with ASD demonstrate reduced spontaneous mimicry to facial expressions of basic emotions, although voluntary imitation remains intact (McIntosh, Reichmann-Decker, Winkielman, & Wilbarger, 2006; Oberman, Winkielman, & Ramachandran, 2009; Stel, van den Heuvel, & Smeets, 2008). However, evidence for a deficit is mixed, with other studies reporting intact or heightened spontaneous mimicry to emotional

faces in adults with ASD (Magnée, De Gelder, Van Engeland, & Kemner, 2007; Schulte-Rüther et al., 2017). Methodological factors could account for the mixed findings, as studies showing reduced mimicry have used passive observation paradigms, whereas studies showing no deficit have used more attention-demanding tasks to control for the possible lack of orientation or attention to facial stimuli in ASD.

Fewer studies have directly assessed emotional contagion in ASD by measuring one's subjective experience of shared emotions. Stel et al. (2008) reported that the mimicry of emotional facial expressions facilitated a corresponding experience of the associated emotion in controls, but not in individuals with ASD. In another study, children were shown short video clips of characters experiencing emotions in different situations, then asked to label the character's emotion and describe how they themselves felt in response (Yirmiya, Sigman, Kasari, & Mundy, 1992). The authors reported that compared to controls, children with ASD described feeling emotions that were less congruent to the emotions perceived in characters. Similarly, individuals with ASD demonstrated less emotional contagion than controls when viewing sad and happy faces, by selecting a "neutral" category to indicate how they felt (Schulte-Ruther et al., 2011).

Atypical demonstrations of empathic concern have also been reported in ASD. Studies assessing this form of affective empathy have utilised the "examiner distress" paradigm (Sigman, Kasari, Kwon, & Yirmiya, 1992), where the examiner pretends to hurt themselves (e.g., knock knee on table), expressing their pain through facial expressions, vocalisations (e.g., "ouch!") and actions (e.g., rubbing knee). Compared to controls, children with ASD have been reported to demonstrate less behavioural responsiveness to the examiner's distress, including less frequent looking at the examiner and less disengagement from other activities (e.g., toy

play) to shift focus to the examiner (Charman et al., 1997; Corona, Dissanayake, Arbelle, Wellington, & Sigman, 1998; Scambler et al., 2007; Sigman et al., 1992). Further, Corona et al. (1998) reported that children with ASD showed no increase in heartrate in the distress condition relative to a baseline condition where the examiner demonstrated neutral expressions upon hurting themselves. Atypical physiological responses to distress were also reported in another study, where children with ASD showed decreased heart rate while viewing pictures of people crying or grieving, but increased heart rate when they viewed pictures of neutral expressions (Bölte, Feineis-Matthews, & Poustka, 2008).

In addition to experimental paradigms, self-report measures have been used to assess affective and cognitive empathy in ASD, particularly the Empathy Quotient (EQ; Baron-Cohen & Wheelwright, 2004) and Interpersonal Reactivity Index (IRI; Davis, 1983). The EQ does not have subscales to differentiate the affective and cognitive dimensions of empathy, although it has a two-factor structure that corresponds to each dimension (Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004). Baron-Cohen and Wheelwright (2004) found lower self-ratings of empathy on the EQ for adults with HFA/AS compared to controls, with post-hoc interviews suggesting that their reduced empathy was more cognitive than affective in nature. Specifically, although the HFA/AS group had difficulty interpreting and responding to the behaviours of others, they typically felt remorse when examiners pointed out the consequences of their reduced empathy (e.g., hurting other people's feelings). Low scores for children and adolescents with ASD were replicated in self- and parent-report versions of the EQ (Auyeung, Allison, Wheelwright, & Baron-Cohen, 2012; Auyeung et al., 2009; Johnson, Filliter, & Murphy, 2009). Studies have also found sex differences in EQ scores within ASD groups and controls, with higher empathy in females compared to males (Auyeung et al., 2009; Baron-

Cohen & Wheelwright, 2004). Of note, lower scores on the EQ correlate with higher scores on the AQ (Baron-Cohen & Wheelwright, 2004).

Unlike the EQ, the IRI has subscales that distinguish between cognitive and affective empathy (Davis, 1983). Subscales measuring cognitive empathy include "Perspective Taking" (e.g., ToM) and "Fantasy" (e.g., imaging oneself in fictional situations), while those measuring affective empathy include "Empathic Concern" (e.g., concern for others in distress) and "Personal Distress" (e.g., self-oriented concern in stressful situations). Studies have consistently shown that individuals with AS score lower than controls on IRI subscales of cognitive empathy (Rogers, Dziobek, Hassenstab, Wolf, & Convit, 2007; Rueda, Fernández-Berrocal, & Baron-Cohen, 2015). However, findings on IRI subscales of affective empathy are mixed. One study showed a trend towards lower scores on the Empathic Concern subscale and higher scores on Personal Distress for the AS group compared to controls (Rogers et al., 2007), whereas another study showed no group differences on both subscales (Rueda et al., 2015).

3.3.2. Neural bases of empathy

The "shared network hypothesis" of empathy suggests that individuals can share and understand the emotions of others by recruiting brain regions that represent their own experience of the same emotion (Gallese, 2003; McCall & Singer, 2013). Examples of these brain regions include the ACC/MCC and anterior insula, which are consistently found to activate during the perception of pain and disgust, and to the direct experience of these emotions (Botvinick et al., 2005; Jabbi, Swart, & Keysers, 2007; Lamm, Decety, & Singer, 2011; Saarela et al., 2007; Singer et al., 2004; Wicker et al., 2003). Studies have also shown that activation in the ACC and insula (elicited by the perception of pain and disgust) correlate

positively with self-ratings of affective empathy on the Empathic Concern and Personal Distress subscales of the IRI (Jabbi et al., 2007; Saarela et al., 2007; Singer et al., 2004). Of note, a meta-analysis of fMRI studies assessing empathy (Fan, Duncan, de Greck, & Northoff, 2011) revealed consistent clusters of activation in the ACC-anterior MCC-supplementary motor area (SMA) and bilateral insula (Figure 3.2), irrespective of task design (e.g., affective/perceptual, cognitive/evaluative) or the type of emotion assessed (e.g., whether empathising with pain, fear, happiness, disgust, or anxiety). As such, the authors concluded that the ACC-MCC-SMA and bilateral insula comprise a core neural network for empathy.

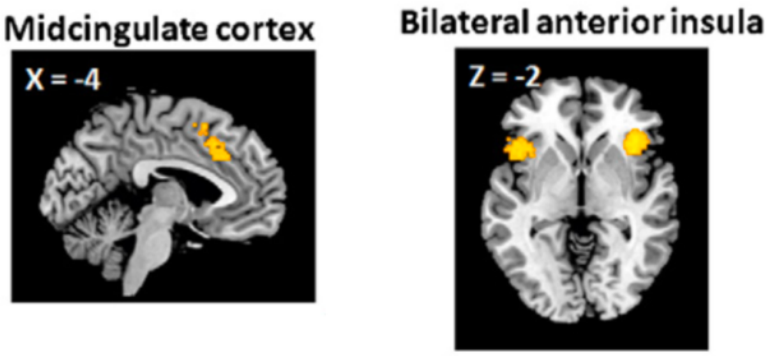


Figure 3.2. Brain regions showing consistent clusters of activation across a meta-analysis of 40 fMRI studies, which assessed affective and cognitive empathy for various emotional states (e.g., pain, disgust, fear, anxiety, happiness). The cluster at the MCC also extends ventrally to the ACC and dorsally to the SMA (not pictured in this sagittal slice). Image source: Fan et al. (2011)

Some researchers have also linked the mirror neuron system (MNS) to empathy, although it is traditionally discussed in the context of action understanding and imitation (Braadbaart, de Grauw, Perrett, Waiter, & Williams, 2014; Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Gallese, 2001; Iacoboni, 2009; Leslie, Johnson-Frey, & Grafton, 2004; Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008). The MNS consists of regions that commonly activate during the observation and execution of goal-directed actions, including the IFG (pars opercularis), ventral premotor cortex, IPL, and STS (Iacoboni et al., 2005; Molenberghs, Brander,

Mattingley, & Cunnington, 2010; Rizzolatti, 2005). In the context of empathy, Carr et al. (2003) reported that core MNS structures (i.e., IFG and STS), the anterior insula, and amygdala collectively activate during the perception and imitation of emotional faces. Accordingly, they reasoned that "empathic resonance" (i.e., affective empathy) occurs when action representation in the MNS modulates emotional processing in limbic areas via the insula, which serves as a relay between both networks. Their findings were replicated by Pfeifer et al. (2008), who additionally reported that activity in the IFG, amygdala, and insula correlated positively with self-ratings of affective empathy (e.g., Empathic Concern and Personal Distress subscales of the IRI) and interpersonal skills (see also van der Gaag, Minderaa, & Keysers, 2007). Within the auditory domain, Aziz-Zadeh et al. (2010) also reported that the perception and production of emotional vocalisations elicited common activation in the IFG, which in turn correlated positively with self-ratings of affective empathy on the Personal Distress subscale of the IRI (see also Warren et al., 2006).

Few fMRI studies have assessed the neural correlates of empathic processing in ASD, yielding mixed findings for atypical activation in the relevant brain networks. One pain-related study reported that individuals with ASD and controls demonstrated similar levels of activation in the ACC and anterior insula while observing others in pain, suggesting that affective empathy is preserved in ASD (Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2007). Another study on pain perception revealed no differences in insula activation between the ASD and control groups, particularly when self-ratings of alexithymia were controlled (Bird et al., 2010). In contrast, Gu et al. (2015) reported that individuals with ASD demonstrated hyperactivation of the insula and increased skin conductance response when perceiving others in pain, suggesting atypical cortical and autonomic responses to affective empathy. Another study by Krach et al. (2015) revealed that individuals with ASD demonstrated hypoactivation of the insula when

observing others suffering specifically from social pain (e.g., embarrassment), although they showed typical brain activation to physical pain scenarios. Interestingly, the authors also found that the ASD group's self-reported intensity of the social pain experience did not correlate with insula activity, but to activation in the hippocampus, suggesting that they relied on memory for social rules to compensate for reduced empathy.

Researchers have also hypothesised that "broken mirror neurons" account for reduced empathy in ASD (Oberman & Ramachandran, 2007; Ramachandran & Oberman, 2006; Williams, Whiten, Suddendorf, & Perrett, 2001). In support of this hypothesis, Dapretto et al. (2005) found that children with ASD demonstrated no significant activation in the MNS (specifically the bilateral IFG) and reduced insula and amygdala activation (relative to controls) while observing and imitating emotional faces. Lower activation in these regions correlated with higher levels of social impairment on clinical measures of ASD. In another fMRI study, Greimel et al. (2010) found that adolescent boys with ASD showed reduced activation in the IFG when inferring their own emotions in response to the facial expressions of others (e.g., "how do you feel when you look at that face?"). Relative to controls, the ASD group also reported experiencing emotions that were less congruent to the facial expressions observed (e.g., feeling "neutral" or "sad" in response to happy faces), leading the authors to infer an association between reduced affective empathy and "aberrant mirroring mechanisms" in ASD. However, these findings were not replicated by Schulte-Ruther et al. (2011), who used the same paradigm, but reported no differences in IFG activation between adults with ASD and controls.

It is important to note that there is debate as to whether atypical activation within regions ascribed to the MNS can fully account for difficulties with empathising in ASD, especially

since little is known about how mirror neurons serve social functions in the first place (Baird, Scheffer, & Wilson, 2011; Fan, Decety, Yang, Liu, & Cheng, 2010; Hamilton, 2013). For example, while the MNS is associated with the perception-action coupling of emotional expressions, it is unclear whether it also evokes a congruent emotional response in the self and how it facilitates the understanding of other people's affective states (Lamm & Majdandžić, 2015). Further, the perception-action coupling paradigms in empathy-related studies have been limited to voluntary imitation (e.g., Carr et al., 2003; Pfeifer et al., 2008), and it is unclear whether the MNS is also associated with the spontaneous mimicry of emotional expressions. Importantly, Fan et al.'s (2011) meta-analysis showed that core regions of the MNS are not consistently activated across fMRI studies related to empathy. Evidence for an association between atypical MNS activation and other forms of social communication deficits in ASD (e.g., poor imitation and action understanding) is also inconsistent, suggesting that MNS dysfunction is not a hallmark of the disorder (see Hamilton, Brindley, & Frith, 2007 for a review).

3.3.3. Expression in the BAP

Studies have assessed empathising in family members of individuals with ASD. Grove, Baillie, Allison, Baron-Cohen, and Hoekstra (2014) found a four-factor structure for empathy (i.e., cognitive empathy, emotional empathy, social skills, performance-based measurement) from scores on questionnaires (e.g., EQ, AQ) and social cognitive tasks (e.g., Eyes Test, emotion recognition tests) administered to individuals with ASD, their parents and controls from the general population. They reported that individuals with ASD and their parents showed lower mean latent factor scores for all four empathy factors compared to controls, with parents showing intermediate difficulties (i.e., ASD < parents < controls; see also Grove, Baillie, Allison, Baron-Cohen, & Hoekstra, 2013). Another study revealed that fathers, but not

mothers, of individuals with ASD scored lower on the EQ compared to controls (Sucksmith, Allison, Baron-Cohen, Chakrabarti, & Hoekstra, 2013).

One study revealed no deficit in "empathic responding" in younger (high-risk) siblings of children with ASD (McDonald, Murphy, & Messinger, 2017). On behavioural observation, high-risk siblings and controls were rated to have similar levels of personal distress, empathic concern, or prosocial behaviour when reacting to an examiner's distress (e.g., when examiner pretended to hurt herself by dropping objects on her foot). Surprisingly, high-risk siblings were also rated to have higher levels of empathic concern than controls on a parent-report measure. These findings are consistent with a study by Tsang et al. (2016), which showed that siblings of individuals with ASD and controls did not differ in their levels of parent-reported affective empathy and attention to an examiner's distress. However, Tsang et al. (2016) reported ToM deficits in siblings, suggesting a discrepancy between levels of affective and cognitive empathy in the BAP.

To date, only one neuroimaging study has examined the neural correlates of empathy in the BAP. In the fMRI study by Greimel et al. (2010) described above (p. 60), a sample of fathers were tested on the same empathy tasks as their adolescent sons with ASD. Like the ASD group, fathers demonstrated reduced activation in the fusiform gyrus compared to controls when identifying the facial emotions of others (cognitive empathy), suggesting a potential neurobiological endophenotype for empathising in ASD. Fathers also showed reduced activation in the amygdala during this task. Despite this, fathers demonstrated intact behavioural performance, suggesting a reliance on strategies to compensate for atypical brain activation underlying cognitive empathy. In contrast, fathers did not show atypical brain

activation when inferring their own emotional responses to the stimuli, indicating normal brain activation underlying affective empathy.

Within the general population, higher self-ratings of the BAP correlate with lower self-ratings of general empathy (i.e., composite score on measures of cognitive and affective empathy; Jamil et al., 2017; Lamport & Turner, 2014). Lamport and Turner (2014) reported that weaker empathy skills also mediated the relationship between higher levels of the BAP (i.e., total BAPQ scores) and attachment anxiety and avoidance in romantic relationships in undergraduate students. Similarly, Jamil et al. (2017) found that reduced empathy mediated the relationship between higher levels of pragmatic language difficulties (on the BAPQ) and lower enjoyment and duration of friendships in undergraduate students.

3.4. Face Processing

3.4.1. Deficits in identity recognition

Face processing is one of the most widely researched components of social cognition in ASD. Much attention has been given to the processing of facial emotional expressions in ASD (Section 3.4.2.), although several studies have also examined perceptual abilities relating to face identity recognition (Golarai, Grill-Spector, & Reiss, 2006; Sasson, 2006; Tang et al., 2015; Weigelt, Koldewyn, & Kanwisher, 2012). A systematic review of 91 behavioural studies on face identity recognition revealed mixed findings, with approximately 50% of studies reporting a deficit in ASD compared to control groups (Weigelt et al., 2012). The authors noted that recognition deficits tend to emerge on tasks with a memory component, such as matching tasks or same-different tasks, in which the stimuli to be discriminated are presented sequentially (with a short time delay in-between) rather than simultaneously (see also Tang et al., 2015). Importantly, individuals with ASD are able to recognise other visual objects (e.g.,

buildings, cars, animals, non-facial social stimuli like bodies) at similar levels to controls, even on tasks that impose memory demands (Kuusikko-Gauffin et al., 2011; Weigelt et al., 2012; Weigelt, Koldewyn, & Kanwisher, 2013). This suggests that face recognition deficits are domain-specific and unlikely to be caused by generalised deficits in visual memory or visual perception (Weigelt et al., 2013).

Studies have employed various paradigms to assess whether individuals with ASD have a feature-based rather than holistic or configural style for processing faces (Watson, 2013; Weigelt et al., 2012). One such paradigm is the "face inversion task", where participants make judgments about faces presented in an upright or inverted/upside-down position (Yin, 1969). Holistic processing of faces would result in better identification of upright versus inverted faces, as expected for typically-developing individuals (Tanaka & Simonyi, 2016; Valentine, 1988). Studies generally show a normal face inversion effect in individuals with ASD, suggesting intact holistic face processing (Falck-Ytter, 2008; Hedley, Brewer, & Young, 2015; Nishimura, Rutherford, & Maurer, 2008; Scherf, Behrmann, Minshew, & Luna, 2008; Tavares, Mouga, Oliveira, & Castelo-Branco, 2016; Teunisse & de Gelder, 2003; Weigelt et al., 2012). This contradicts expectations for a local processing bias in ASD, as posited by the "weak central coherence" theory of ASD (Frith & Happé, 1994; Happé & Frith, 2006). More specifically, the weak central coherence theory suggests that individuals with ASD have strong attention to detail, which can interfere with their ability to integrate features into a coherent whole (Frith & Happé, 1994; Happé & Frith, 2006).

Holistic processing is also assessed with the "composite face task" (Figure 3.3a), where the top and bottom halves of two different faces are combined to form a new face in an aligned or misaligned condition (Young, Hellawell, & Hay, 1987). In its standard version, participants

identify the original face that matches the cued half of the composite face while ignoring the other half, with better performances expected in the misaligned versus aligned condition (Tanaka & Simonyi, 2016; Young et al., 1987). Some researchers have shown a reduced composite effect in ASD, where the misaligned condition does not provide an advantage for face identity recognition (Gauthier, Klaiman, & Schultz, 2009; Teunisse & de Gelder, 2003), while others have shown an intact composite effect (Nishimura et al., 2008).

A more direct way to assess holistic versus feature-based face processing is using the "part-whole task" (Figure 3.3b; Tanaka & Simonyi, 2016). In this task, participants are required to match a target face with two forced-choice alternatives in a whole-face test condition (e.g., target face vs. foil face that differs from target by one facial feature) or an isolated-part test condition (e.g., eyes/nose/mouth from target face vs. foil face, presented in isolation). There is evidence to suggest that individuals with ASD, like controls, show a whole-face advantage, thereby supporting the idea of intact holistic face processing in ASD (Faja, Webb, Merkle, Aylward, & Dawson, 2009; Joseph & Tanaka, 2003; López, Donnelly, Hadwin, & Leekam, 2004; Wolf et al., 2008). However, the whole-face advantage appears to be restricted to certain conditions in affected individuals (Joseph & Tanaka, 2003; López et al., 2004; Wolf et al., 2008). For example, one study found that individuals with ASD perform better on the whole-face rather than isolated-part condition only when cued to look at the feature that differed between the target and foil face (e.g., "Look at the mouth"; López et al., 2004). Studies have also shown that individuals with ASD demonstrate a whole-face advantage only when discriminating faces based on the mouth, but not the eyes (Joseph & Tanaka, 2003; Wolf et al., 2008).

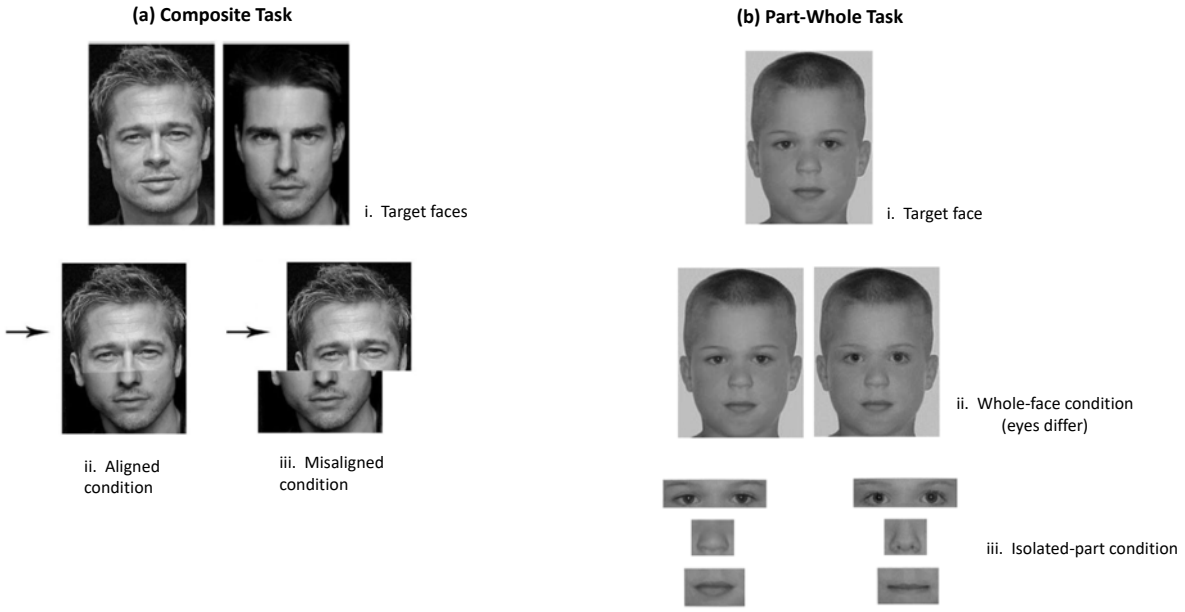


Figure 3.3. Examples of tasks measuring holistic face processing. Image sources: Joseph and Tanaka (2003), Tanaka and Sung (2016)

Of note, typically-developing individuals rely heavily on information from the eyes to make judgments about face identity, whereas individuals with ASD do not show this preference (Tanaka & Sung, 2016). For example, studies using eye tracking have shown that individuals with ASD attend to the mouth but avoid the eyes in static and dynamic displays of faces, consistent with the hallmark feature of poor eye contact in ASD (Dalton et al., 2005; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Neumann, Spezio, Piven, & Adolphs, 2006; Pelphrey et al., 2002; Spezio, Adolphs, Hurley, & Piven, 2007). Participants also perform worse on tasks that require participants to make judgments about others (e.g., ToM, emotions, gender discrimination, same/different simple face perception) based on information in the eyes alone (Baron-Cohen et al., 2001; Best, Minshew, & Strauss, 2010; Harms, Martin, & Wallace, 2010; Joseph & Tanaka, 2003; Riby, Doherty-Sneddon, & Bruce, 2009).

3.4.2. Deficits in emotion recognition

The face conveys important information about one's affective state, as already alluded to in the review on empathising (Section 3.3). The majority of emotion recognition studies in ASD has focused on the face over other modalities of emotional expression, like the voice and body postures. The functional significance of emotional facial expressions was first noted by Darwin (1872) who suggested that they were outward manifestations of inner affective states, serving as ethological signals for social communication. Darwin observed parallels between emotions expressed by humans and animals, and suggested that emotional expressions in humans evolved through the process of natural selection. Importantly, he also proposed the universality of emotional facial expressions, where humans express a discrete set of emotions in the same manner (likely eliciting similar physiological processes and activating specific muscle groups), regardless of race or culture (Ekman, 2009).

The universality of emotions was empirically supported by a series of studies by Ekman and colleagues (1969, 1971), giving rise to the concept of "basic emotions" in psychology (see also Ekman, 1992; Izard, 1992). Specifically, they revealed that photographs of faces expressing the six emotions of anger, disgust, fear, happiness, sadness, and surprise were recognised at high accuracy rates across cultures, including communities that were preliterate and those that had minimal exposure to cultures other than their own (Ekman & Friesen, 1971; Ekman et al., 1987; Ekman, Sorenson, & Friesen, 1969). Figure 3.4 shows examples of basic facial expressions from a widely used, validated battery of emotional face stimuli, namely Ekman's Pictures of Facial Affect (Ekman & Friesen, 1976). Moreover, studies have shown that individuals from different cultures spontaneously exhibit similar facial expressions corresponding to the six basic emotions in experimental settings designed to elicit emotions (Matsumoto, Keltner, Shiota, O'Sullivan, & Frank, 2008).

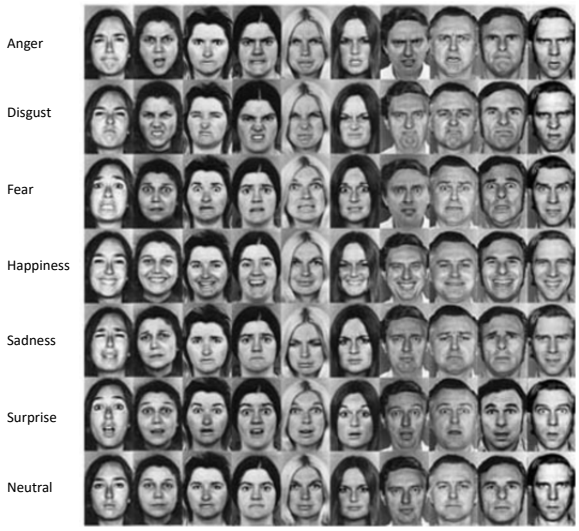


Figure 3.4. Photographs of the six basic emotions and a neutral category from the Pictures of Facial Affect battery (Ekman & Friesen, 1976). Image source: Young, Perrett, Calder, Sprengelmeyer, and Ekman (2002)

Research on basic emotional face processing in ASD has yielded mixed findings, with several studies reporting deficits and others reporting intact ability (Harms et al., 2010; Lozier, Vanmeter, & Marsh, 2014; Uljarevic & Hamilton, 2013). Inconsistencies are influenced by differences in sample size, participant demographics (e.g., age, IQ), control group matching, task design, and the possible use of compensatory strategies (Harms et al., 2010; Lozier et al., 2014; Uljarevic & Hamilton, 2013). Moreover, some studies have reported generalised facial emotion recognition deficits with accuracy measures combined across multiple emotions (Lozier et al., 2014), while others have reported specific deficits for negative emotions like anger, disgust, fear, and sadness (Ashwin, Chapman, Colle, & Baron-Cohen, 2006; Balconi, Amenta, & Ferrari, 2012; Boraston, Blakemore, Chilvers, & Skuse, 2007; Wallace et al., 2011) or more belief-based emotions, like surprise (Baron-Cohen, Spitz, & Cross, 1993).

Given these inconsistencies, two meta-analyses (N = 791-932 participants with ASD across 43-48 studies) were performed to clarify the integrity of basic emotion recognition in ASD (Lozier

et al., 2014; Uljarevic & Hamilton, 2013). Both provided evidence for a generalised emotion recognition deficit, with Uljarevic and Hamilton (2013) reporting a strong mean effect size (0.80) which was reduced to moderate levels (0.41) after accounting for publication bias. Lozier et al. (2014) reported that while emotion recognition deficits were found across all six basic emotions, deficits were most severe for anger, fear, and surprise. In relation to anger, studies have found that children with more severe ASD symptoms tend to show greater avoidance of angry faces compared to those with milder symptoms, likely because angry faces are highly arousing and elicit distress (García-Blanco et al., 2017; Matsuda, Minagawa, & Yamamoto, 2015). Impaired recognition of fearful faces has been linked to amygdala dysfunction in ASD (Chris Ashwin et al., 2006; Howard et al., 2000; see also Section 3.4.3), while impaired recognition of surprise has been linked to ToM difficulties (Baron-Cohen et al., 1993).

Uljarevic and Hamilton (2013) reported that the level of ASD deficit was similar on emotion matching and emotion labelling tasks, suggesting a minimal effect of task design on performance. On emotion matching tasks, participants match facial emotions to other modalities of expression (e.g., voice, body language) or contextual information (Fein, Lueci, Braverman, & Waterhouse, 1992; Hobson, 1986; Leung, Ordqvist, Falkmer, Parsons, & Falkmer, 2013; Lindner & Rosén, 2006; Ozonoff, Pennington, & Rogers, 1990; Philip et al., 2010; Taylor, Maybery, Grayndler, & Whitehouse, 2015). On emotion labelling tasks, participants view facial emotions and assign a corresponding emotion category from a list of labels in a forced choice format (Boraston et al., 2007; Clark, Winkielman, & McIntosh, 2008; Grossman, Klin, Carter, & Volkmar, 2000; Spezio et al., 2007) or an unprompted, free naming format (Dyck, Ferguson, & Shochet, 2001; Macdonald et al., 1989; Rump, Giovannelli, Minshew, & Strauss, 2009). Emotion matching tasks require judgments based on comparison

between physical features, whereas emotion labelling tasks require judgments based on intact verbal skills (Uljarevic & Hamilton, 2013). Similar levels of reduced performance on both tasks therefore suggest a genuine emotion recognition deficit in ASD, which is not primarily driven by perceptual or linguistic demands (Uljarevic & Hamilton, 2013).

Uljarevic and Hamilton (2013) also reported no effect of IQ on facial emotion recognition in ASD, suggesting that deficits are not specific to low-functioning groups. However, the authors acknowledged that further research is required to examine the relationship between IQ and emotional face processing, since most studies in their meta-analysis matched ASD and control groups based on IQ (e.g., level of performance expected on the basis of mental age rather than chronological age). It is also possible that individuals with higher IQ are more capable of acquiring compensatory strategies to improve their performance and identify facial emotions at similar levels to controls (Capps, Yirmiya, & Sigman, 1992; Harms et al., 2010; Lozier et al., 2014; Teunisse & de Gelder, 2001). For example, individuals with HFA can use verbal mediation to achieve high performance on emotion labelling tasks (Grossman et al., 2000; Teunisse & de Gelder, 2001). Another form of compensation relates to memorising facial features associated with specific emotions (e.g., frown and lowered eyebrows represent sadness), although this "rule-based" strategy may limit generalisation across less prototypical expressions (Harms et al., 2010). Accordingly, individuals with HFA are more likely than controls to perceive artificially exaggerated emotional facial expressions as being more realistic than natural faces (e.g., the larger the frown, the sadder the person), likely supporting a feature-based rather than configural form of processing (Rutherford & McIntosh, 2007; Walsh, Vida, & Rutherford, 2014). Studies using the "Bubbles" method (where only small portions of the face are revealed) have shown that when identifying emotions in obscured faces,

individuals with HFA fixate on the mouth rather than eyes more often and for longer durations than controls (Neumann et al., 2006; Spezio et al., 2007).

In their meta-analysis, Lozier et al. (2014) examined the moderating role of age on facial emotion recognition in ASD by comparing studies that assessed paediatric (< 18 years) and adult samples. The authors reported a linear effect of age, where deficits were least severe in young children, intermediate in adolescents, and most severe in adults, which is the opposite pattern expected in typical development. Most studies included in their paper were cross-sectional, with only one longitudinal study by Rump et al. (2009) reporting direct comparisons across age groups. Rump et al. (2009) assessed emotion recognition using brief video displays of facial expressions that varied in subtlety. They found that unlike controls, who showed age-related improvements, the ASD group did not show any improvement or decline, with stable performance observed from childhood to adulthood. They reasoned that the lack of age-related improvement could be due to reduced configural processing and poor abstraction of subtle expressions that differ from more prototypical expressions.

Individuals with ASD also have difficulties identifying neutral faces within the context of an emotion recognition task, confusing them with basic emotions at higher rates than controls (Eack, Mazefsky, & Minshew, 2015; Vannetzel, Chaby, Cautru, Cohen, & Plaza, 2011). Poor recognition of neutral faces has also been associated with lower emotional intelligence and social communication skills in ASD (Eack et al., 2015; Xu et al., 2015). Overall, these findings suggest a fundamental emotion recognition deficit where individuals with ASD are less able to differentiate between the presence or absence of emotions in stimuli that serve an ambiguous purpose in emotional contexts. Interestingly, one study also reported that individuals with ASD attributed negative valence to neutral faces and misinterpreted happy faces as being neutral

(Eack et al., 2015), which may support a negative information-processing bias in ASD (e.g., Herrington et al., 2017).

In addition, individuals with ASD show recognition deficits for complex emotions, which are generally more difficult to recognise than basic emotions (Adolphs, Sears, & Piven, 2001; Baron-Cohen et al., 1997; Capps et al., 1992; Fridenson-Hayo et al., 2016; Golan, Baron-Cohen, & Hill, 2006). Complex emotions are considered by some researchers to be "non-basic", since they rely more heavily on cognitive evaluation rather than basic physiological reactions and show more cultural and individual variation (Griffiths, 2003; Oatley & Johnson-Laird, 1987; although see Ortony & Turner, 1990 for a critical view on basic emotions). Examples include jealousy, remorse, anxiety, pride, and embarrassment, which reflect complex mental states (e.g., beliefs, intentions, expectations) that result from appraisals about oneself in reference to others (Oatley & Johnson-Laird, 1987) and require intact ToM to discern (e.g., Eyes Task; Baron-Cohen et al., 1997; Baron-Cohen et al., 2001). Complex emotions may comprise a combination of basic emotions, such as jealousy comprising elements of anger, sadness, and fear (Ekman, 1992; Oatley & Johnson-Laird, 1987).

Golan, Baron-Cohen, and Hill (2006) developed the Cambridge Mindreading (CAM) Face-Voice Battery to assess complex emotion recognition in video clips of the face and voice recordings of speech prosody in separate tasks. They found that adults with AS had difficulty recognising 12 out of 20 complex emotions (e.g., insincere, subservient, intimate, exonerated) across both tasks. Performance on the CAM correlated with performance on the Eyes Task and the revised version of the Reading the Mind in the Voice Task (Golan et al., 2007), which assess similar processes. Higher scores on the CAM also correlated with higher symptom severity on the AQ. Fridenson-Hayo et al. (2016) reported that individuals with HFA from

Israel, Britain, and Sweden were worse than controls at recognising complex emotions in the face and other expressive modalities (e.g., speech prosody, body language), indicating cross-cultural effects.

Finally, it is important to note that poor facial emotion recognition in ASD can be influenced by alexithymia. As aforementioned, alexithymia is a subclinical condition characterised by difficulties in understanding and describing one's own emotional state (Taylor & Bagby, 2004). Alexithymia is substantially more prevalent in ASD (40-65%) than the general population (10%), although it is not a diagnostic feature of ASD (Berthoz & Hill, 2005; Hill, Berthoz, & Frith, 2004). Studies have shown that higher levels of alexithymia are associated with lower general emotion recognition ability (across face and voice modalities) in individuals with ASD and healthy controls (Bird & Cook, 2013; Cook, Brewer, Shah, & Bird, 2013; Grynberg et al., 2012; Heaton et al., 2012; Kätsyri, Saalasti, Tiippana, von Wendt, & Sams, 2008; Ketelaars, In't Velt, Mol, Swaab, & van Rijn, 2016). Interestingly, Cook et al. (2013) found that lower self-ratings of alexithymia but not autism traits (i.e., scores on the AQ) predicted poor precision of facial emotion recognition in ASD and controls. Further, they found no significant group difference in the precision of facial emotion recognition when both groups were matched on levels of alexithymia, suggesting that alexithymia but not ASD per se contributed to facial emotion recognition deficits (see also Kätsyri et al., 2008). It is therefore possible that mixed findings of an ASD deficit in facial emotion recognition ability are influenced by different levels of alexithymia across different samples of ASD and controls (Bird & Cook, 2013).

3.4.3. Face processing system

Several brain regions have been implicated in face processing, with the fusiform face area (FFA) in the lateral middle fusiform gyrus being the most well-known. In their seminal fMRI

study, Kanwisher, McDermott, and Chun (1997) reported face selectivity in the bilateral FFA, showing that activation in these regions responded more strongly to the passive viewing of intact faces over scrambled faces, objects, or other body parts. Face selectivity of the FFA, shown most consistently in the right hemisphere, has been replicated in other fMRI face processing paradigms in the general population (Gauthier et al., 2000; Grill-Spector, Knouf, & Kanwisher, 2004; Kanwisher, Tong, & Nakayama, 1998; Kanwisher & Yovel, 2006; McCarthy, Puce, Gore, & Allison, 1997) and studies of individuals with prosopagnosia (Barton, Press, Keenan, & O'Connor, 2002; Furl, Garrido, Dolan, Driver, & Duchaine, 2010; Zhang, Liu, & Xu, 2015).

The FFA relies on integration with other face selective regions to support face processing (Rossion et al., 2003; Schiltz et al., 2006). These include the lateral inferior occipital gyrus (IOG; also known as the "occipital face area") and the posterior STS, which together with the FFA, form the "core system" for face processing, as shown in Figure 3.5 (Haxby, Hoffman, & Gobbini, 2000; Ishai, 2008). The IOG and FFA are considered to be responsible for the recognition of face identity, which constitutes relatively invariant physical attributes (Haxby et al., 2000; Kanwisher et al., 1997; Schiltz et al., 2006), while the STS serves changeable aspects of the face like direction of eye gaze, speech-related movements, and emotional expressions (Puce et al., 2003; Schobert, Corradi-Dell'Acqua, Frühholz, van der Zwaag, & Vuilleumier, 2018). DTI analyses have shown white matter connectivity between the FFA and IOG (more pronounced in the right hemisphere), whereas the STS is not directly connected to either structure, but rather to frontoparietal regions outside the core system (Gschwind, Pourtois, Schwartz, Van De Ville, & Vuilleumier, 2012; Pyles, Verstynen, Schneider, & Tarr, 2013).

In addition to the core system, researchers have proposed an "extended" system of distributed regions, including the amygdala, IFG, OFC, and anterior temporal lobe (Haxby et al., 2000; Ishai, 2008). These regions serve other cognitive functions and are not selective to faces, although they are often recruited with the core system to facilitate the emotional and social aspects of face recognition (Haxby et al., 2000). Among the core regions, the FFA is considered the primary causal input to the extended system, with connections to the amygdala to support emotional face processing, the IFG to support to support cognitive evaluation, and the OFC to support reward processing related to beauty or sexual attraction (Fairhall & Ishai, 2007). The FFA and IOG are also connected to the anterior temporal lobes, which are semantic hubs for information about personal identity (Anzellotti, 2017; Pyles et al., 2013).

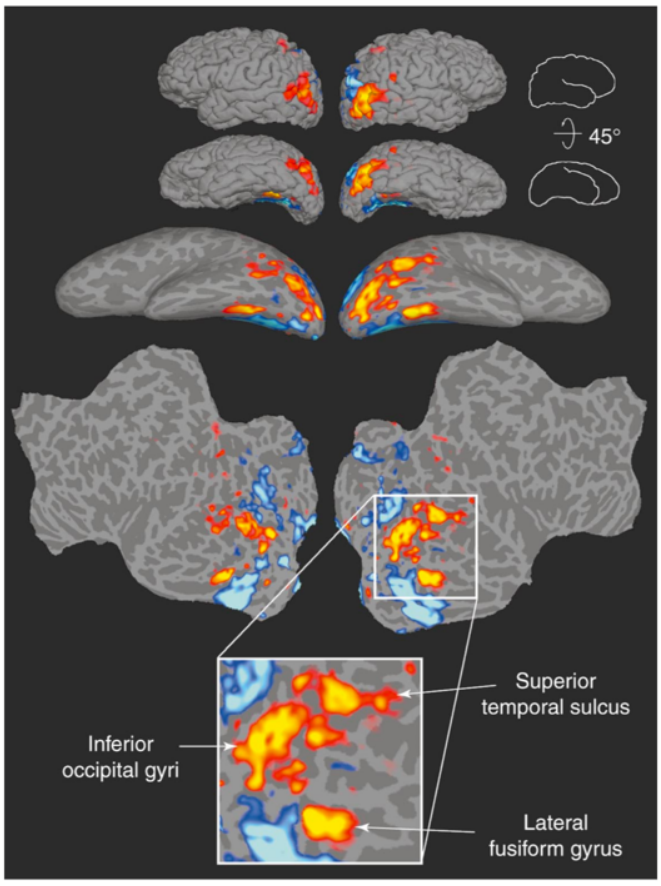


Figure 3.5. The core system for face processing. The fourth row shows the entire cortex flattened into a two-dimensional image. Image Source: Haxby et al. (2000)

Atypical functioning of the core and extended face processing systems has been widely documented in ASD (Harms et al., 2010; Nomi & Uddin, 2015). Individuals with ASD consistently show reduced activation in the fusiform gyrus (FFA and broader regions), IOG, STS, and amygdala in response to passively viewing faces, or on tasks assessing face identity recognition (e.g., judgments about similarities/differences, faces versus objects, gender; Nickl-Jockschat et al., 2015; Nomi & Uddin, 2015; Pierce, Müller, Ambrose, Allen, & Courchesne, 2001; Schultz, 2005). Interestingly, some studies have shown that individuals with ASD process faces using networks for more generalised object perception, suggesting that they process facial features in terms of their visual properties rather than their social relevance (Humphreys, Hasson, Avidan, Minshew, & Behrmann, 2008; Koshino et al., 2008; Scherf, Luna, Minshew, & Behrmann, 2010; Schultz, Gauthier, Klin, & et al., 2000). Studies have also shown that relative to controls, the core and extended face processing systems in ASD are more responsive to objects and non-human faces (e.g., cartoon characters, animals) compared to human faces (Grelotti et al., 2005; Whyte, Behrmann, Minshew, Garcia, & Scherf, 2016).

Studies have also reported that individuals with ASD show hypoactivation in the fusiform gyrus and IOG on emotion matching tasks (see Nomi & Uddin, 2015 for a review). Atypical activation of the amygdala has also been consistently implicated across emotion-related studies, with evidence for both hypoactivation (Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007; Corbett et al., 2009; Hadjikhani et al., 2007) and hyperactivation (Dalton et al., 2005; Kleinhans et al., 2009; Kliemann, Dziobek, Hatri, Baudewig, & Heekeren, 2012; Monk et al., 2010; Swartz, Wiggins, Carrasco, Lord, & Monk, 2013). Hyperactivation of the amygdala has suggested reduced habituation or adaptation to negative emotional faces (and also neutral ones) in ASD (Kleinhans et al., 2009; Swartz et al., 2013). This implies that faces may be percieved as more arousing or aversive to individuals

with ASD compared to controls (Kleinhans et al., 2009; Swartz et al., 2013). Hyperactivation of the amygdala to faces also correlates with higher levels of social communication deficits (Kleinhans et al., 2009; Swartz et al., 2013), social anxiety (Kleinhans et al., 2010), higher threat ratings to neutral faces (Tottenham et al., 2014), and increased eye gaze fixation in ASD (Dalton et al., 2005; Kliemann et al., 2012).

Disruptions to functional connectivity between face processing regions have beeen documented in ASD (Kleinhans et al., 2008; Monk et al., 2010; Murphy, Foss-Feig, Kenworthy, Gaillard, & Vaidya, 2012; Wicker et al., 2008). Kleinhans et al. (2008) reported that higher levels of social communication deficits in ASD correlated with reduced right FFA-left amygdala connectivity and increased right FFA-right IFG connectivity during face processing. Wicker et al. (2008) reported that individuals with ASD showed reduced prefrontal-STS connectivity but increased prefrontal-fusiform connectivity on a facial emotion recognition task. The latter could indicate compensatory strategies for the cognitive evaluation of facial stimuli. The authors also reported hypoconnectivity between the occipital cortex and fusiform gyrus, suggesting disruptions within the core system for face processing. Cheng et al. (2015) reported resting-state hypoconnectivity between regions serving face processing (e.g., STS), ToM (e.g., mPFC), and the sense of self (e.g., precuneus) in ASD, which may contribute to difficulties with representing the self in relation to others.

3.4.4. Expression in the BAP

Atypical face processing forms part of the BAP in family members of individuals with ASD (Wallace et al., 2010; Wilson et al., 2010). Wilson et al. (2010) reported that parents performed worse than controls on a standardised face memory task assessing identity recognition. They also reported that performance on a face matching task correlated between mothers and

children with ASD, which suggests a hereditary basis for face recognition ability in ASD. Wallace et al. (2010) reported that parents and siblings were worse than controls, but better than individuals with ASD, at recognising unfamiliar faces. On a part-whole task, however, relatives demonstrated a normal whole-face advantage for judging the direction of eye gaze in facial stimuli, suggesting intact holistic face processing (Wallace et al., 2010).

Family members of individuals with ASD also show reduced facial emotion recognition abilities compared to controls, (Hu et al., 2018; Kadak et al., 2014; Oerlemans et al., 2014; Palermo et al., 2006; Wallace et al., 2010), although evidence for a deficit is not consistent across studies (Adolphs et al., 2008; Bölte & Poustka, 2003; Sucksmith et al., 2013). There is some variability in performance between sub-groups of parents. For example, Adolphs et al. (2008) showed differences in face processing strategies between parents with and without aloof BAP traits, where aloof parents relied less on the eyes and more on the mouth to make emotional judgments. In another study, Losh et al. (2009) reported that aloof parents were worse than non-aloof parents and controls at identifying subtle expressions of fear and judging the emotional content of movie scenes based on facial expressions. Aloof parents also rated friendly faces as being less trustworthy or more threatening (Losh et al., 2009). Bölte and Poustka (2003) also reported that first-degree relatives from multiplex families performed worse than those from simplex families, supporting the role of genetic loading on emotion recognition ability.

Atypical neural processing of faces has been reported in family members of individuals with ASD. Compared to controls, parents of individuals with ASD show prolonged latency of event-related potentials (ERPs) over the posterior temporal lobe (i.e., slower neural processing) when viewing faces, but not objects (Dawson et al., 2005). Infant siblings also show atypical

ERPs to direct versus averted eye gaze (Elsabbagh et al., 2009) and to familiar versus unfamiliar faces (Luyster, Wagner, Vogel-Farley, Tager-Flusberg, & Nelson, 2011). One fMRI study reported that school-aged siblings had reduced activity in the fusiform gyrus corresponding to decreased gaze fixation (Dalton et al., 2005), while another showed reduced fusiform activity to emotional faces (Spencer et al., 2011). Reduced fusiform activity in relatives resembles the ASD profile (e.g., Nomi & Uddin, 2015) and may represent a potential neurobiological endophenotype for face processing. Yucel et al. (2015) reported the opposite effect, with parents showing enhanced activity in the fusiform gyrus and amygdala on face memory and emotion recognition tasks. They also reported that parents with aloof BAP traits showed greater activation in the lateral occipital cortex compared to non-aloof parents, which may represent neurobiological compensation for face processing in the BAP.

Within the general population, reduced emotional face processing is associated with higher levels of the BAP. One study reported that university undergraduate students with high AQ scores showed no attentional bias to fearful faces (Miu et al., 2012), consistent with evidence that fearful gaze fails to shift the attention of individuals with ASD (Uono, Sato, & Toichi, 2009). In another study, undergraduate students with high AQ scores showed reduced accuracy and decreased sensitivity for negative emotions (i.e., anger, disgust, sadness), and required more intense displays of emotion for accurate identification (Poljac, Poljac, & Wagemans, 2013). Ingersoll (2010) also showed that higher AQ scores correlated with poorer recognition of angry and sad faces in the general population.

3.5. Chapter Summary

Social cognitive deficits in ToM, empathising, and face processing are among the most common forms of social communication impairments in ASD. Individuals with ASD also show functional abnormalities in sub-networks of the social brain that support these processes.

Some studies have found similar profiles of social cognitive difficulties and atypical brain activation in relatives of individuals with ASD, which constitute aspects of the BAP and support a genetic liability for ASD. Lower performance on social cognitive measures is also linked to higher levels of BAP traits in the general population.

The next chapter introduces another aspect of social cognition, specifically emotional voice processing, which has received less attention in ASD despite its critical role in social communication. It highlights the social significance of emotional voice processing and reviews the literature on the recognition of speech-embedded emotional prosody in ASD and the BAP. It also argues for the use of non-linguistic vocalisations as alternative stimuli for extending behavioural and neuroimaging research on emotional voice processing in ASD and the BAP, which informed the aims of this thesis.

CHAPTER 4

Emotional Voice Processing

Overview: This chapter begins with a broad overview of the vocal communication of emotions, then focuses on how typically-developing individuals and those with ASD decode emotional speech prosody on a behavioural and neurobiological level. Next, it highlights the advantages and implications of using non-linguistic emotional vocalisations (i.e., raw vocal affect bursts) as alternative stimuli to emotional speech prosody to advance research targeting purer markers of emotional voice processing in ASD and the BAP. The aims and hypotheses of this thesis are then stated in the final section of this chapter.

4.1. Vocal Communication of Emotions

4.1.1. Functional significance

Darwin's (1872) pioneering work on emotional expressions in humans and animals was not confined to the face alone, but also extended to the voice. Darwin observed that animals use their voice to signal different affective states (e.g., pleasure, pain, rage) which are accompanied by changes to facial expressions, body postures, and other physiological reactions. Darwin also noted that like animals, acoustic features of the human voice vary under different emotional contexts. Evolutionary views of vocal communication support an "affect induction" account of voice signalling, where individuals express emotions not just to inform a listener about their affective states, but primarily to influence the listener's affect and behaviour in ways that would benefit them (Bachorowski & Owren, 2008; Owren, Rendall, & Ryan, 2010; Pisanski, Cartei, McGettigan, Raine, & Reby, 2016). For example, expressions of positive affect can enhance cooperation, whereas expressions of dominance can elicit submission in competitors during a conflict.

Vocal communication of emotions has been studied in less detail than facial expressions, likely because vocal cues are more difficult to measure, characterise, and control in experimental settings (Juslin & Laukka, 2003; Schirmer & Adolphs, 2017). Nonetheless, the voice presents important advantages for the communication of emotions, as it is omnidirectional and can be transmitted across long distances and discerned by others in the absence of visual cues (Hawk et al., 2009; Scherer, 1994). Vocal emotions are particularly arousing and useful for eliciting attention in situations where immediate action is required (Filippi et al., 2017; Johnstone & Scherer, 2000; Scherer, 1994). Further, the voice is a reliable modality for expressing one's true, underlying affective state (Zuckerman, Larrance, Spiegel, & Klorman, 1981). Specifically, vocal emotions are less susceptible to voluntary control (e.g., suppression or

exaggeration, as in the case of deception or conforming to display rules), and more susceptible to "leakage" (e.g., Ekman & Friesen, 1969), or involuntary acts that reveal the true emotion one wishes to conceal (Zuckerman et al., 1981). Accordingly, studies have found that attention to vocal over facial cues is more critical for emotion recognition in "empathic accuracy" paradigms, which measure interpersonal sensitivity in naturalistic settings (Hall & Schmid Mast, 2007; Kraus, 2017; Zaki, Bolger, & Ochsner, 2009).

4.1.2. Encoding of emotions

Emotions can be encoded, or expressed, in the voice as paralinguistic cues embedded in speech (i.e., prosody or tone of voice; Bänziger & Scherer, 2005; El Ayadi, Kamel, & Karray, 2011; Koolagudi & Rao, 2012) or non-linguistic cues (e.g., laughter, cries, screams; see Section 4.4; Scherer, 1994; Schröder, 2003). The influence of affective states on both types of vocalisations can be discussed within the framework of the "source-filter" theory, which describes the mechanisms of voice production more broadly (Fant, 1960). The source-filter theory originated from the study of speech production but can be generalised to other forms of mammalian vocalisations (Taylor & Reby, 2010). It states that voiced signals result from two main stages of production, which involve different anatomical structures that contribute to different aspects of their acoustic profile (Figure 4.1; Fant, 1960; Taylor & Reby, 2010). Specifically, the larynx serves as the "source" where the voiced signal is generated, while the vocal tract (consisting of air cavities between the larynx and mouth/nose) serves as the "filter" through which the signal is modified before being transmitted to the environment (Fant, 1960). Of note, modern accounts of the source-filter theory have proposed that both stages of vocal production are not always "linear", but can also interact to simultaneously influence voiced signals (see Titze, 2008 for an in-depth discussion).

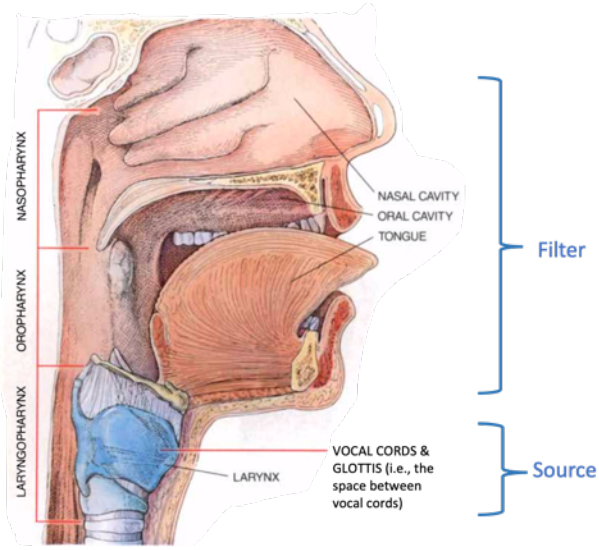


Figure 4.1. Anatomy of voice production corresponding to the source-filter theory. Image source: modified from Sataloff, Heman-Ackah, and Hawkshaw (2007)

According to the source-filter theory, voiced signals are produced at the larynx when air from the lungs exerts pressure against the closed glottis, forcing the vocal cords to push apart and vibrate (Jiang, Lin, & Hanson, 2000). The rate of vocal cord vibration is known as the "fundamental frequency" (F0), perceived as the pitch of the voice. The F0 can be modified by stretching or relaxing the vocal cords or changing the shape and mass of their edges through mechanisms involving the internal and external laryngeal muscles (Jiang et al., 2000; Kappas, Hess, & Scherer, 1991). For example, high F0 results when the edges of the vocal cords are contracted into a sharp and thin shape, whereas low F0 results when the edges are broadened and enlarged (Kappas et al., 1991). Voice quality is also determined at the larynx, as different patterns of glottal constriction determine different types of phonation, including vocal fry (short and sharp glottal opening/closing), falsetto (gradual glottal opening/closing), and breathy voice (incomplete glottal closure; Childers & Lee, 1991). Once generated, voice signals from the larynx travel through the vocal tract, which changes shape according to the position of the pharynx and articulators (e.g., lips, tongue, teeth; Kappas et al., 1991). Different configurations of the vocal tract can dampen or amplify specific ranges of frequencies (known

as resonant frequencies), resulting in changes to the spectral envelope of the voiced signal (Taylor & Reby, 2010). These filtering effects are typically indexed by spectral peaks called "formants", with modulation of lower formants corresponding to the production of phonemes, which are perceived as vowels in speech (Fant, 1960).

The acoustic profile of voiced signals may change according to one's affective state (Kappas et al., 1991). Research on the acoustic features of emotional vocalisations is largely centred on paralinguistic cues speech-embedded prosody (although see Section 4.4.1 for a discussion on the encoding of non-linguistic cues), with measures of F0 being the most widely studied (Bachorowski & Owren, 2008; Koolagudi & Rao, 2012; Scherer, 1986). Other major acoustic features of emotional speech prosody are listed in Table 4.1. Variation in acoustic features in emotional speech prosody is consistently linked to the arousal component of emotions (degree of autonomic activation; Bachorowski & Owren, 1995; Juslin & Laukka, 2001; Laukka, Juslin, & Bresin, 2005; Scherer, 1986). For example, speech prosody for affective states that are highly arousing (e.g., anger, fear, happiness) typically have higher mean F0, F0 variability, intensity, and speaking rate, whereas speech prosody for less arousing affective states (e.g., sadness) are lower on these indices (Bachorowski, 1999; Banse & Scherer, 1996; Scherer, Johnstone, & Klasmeyer, 2003). In contrast, the relationship between acoustic features and the valence component of emotions (degree of pleasantness) in speech prosody is less consistent (Bachorowski & Owren, 2008; Goudbeek & Scherer, 2010; Scherer et al., 2003).

Table 4.1

Major Acoustic Parameters of Vocal Expressions of Emotion

Parameter	Description
F0 mean	Vibration rate of vocal cords averaged over an utterance
F0 variability	Dispersion or standard deviation of F0
F0 perturbation	Slight variations of duration of glottal cycle
F0 range	Difference between highest and lowest F0 in an utterance
F0 contour	F0 values plotted over time (intonation)
F1 mean	Frequency of first formant averaged over an utterance
F2 mean	Frequency of second formant averaged over an utterance
Formant bandwidth	Width of the spectral band containing formant energy
Intensity mean	Energy values averaged over an utterance
Intensity range	Difference between highest and lowest intensity values in an utterance
Intensity variability	Dispersion or standard deviation of intensity
Spectral energy distribution	Relative amount of energy within frequency bands
Spectral slope	Linear regression of energy distribution in the frequency band above 1 kHz
Tremor	Regular modulation of glottal cycle duration
Jitter	Regular or irregular variation of glottal cycle duration
Shimmer	Regular or irregular variation of amplitude maxima in subsequent glottal cycles
Harmonics-to-noise-ratio (HNR)	Ratio between harmonic and aperiodic signal energy

Note. F0 = fundamental frequency; F1 = first formant; F2 = second formant. Table adapted from Scherer (1986) and Scherer et al. (2003).

Researchers have also characterised distinct acoustic profiles for specific emotions (Banse & Scherer, 1996; Hammerschmidt & Jürgens, 2007; Juslin & Laukka, 2003; Laukka et al., 2005; Patel, Scherer, Sundberg, & Björkner, 2010; Rodero, 2011; Sobin & Alpert, 1999). For example, in their seminal study, Banse and Scherer (1996) identified acoustic profiles for 14 emotions, expressed in meaningless speech by professional actors (i.e., "hot" and "cold" anger, panic fear, anxiety, despair, sadness, elation, pride, happiness, interest, boredom, shame, disgust, contempt). A discriminant function analysis classified emotions into their respective categories at above chance levels (53% total accuracy) based on 16 acoustic parameters, including measures of F0, intensity, speech rate, and long-term average spectra. Interestingly, overall accuracy rates and patterns of errors (i.e., confusion between emotions) from the discriminant analysis were similar to those made by human judges (48%), even though the

exact stimuli that were correctly/incorrectly identified differed between the two methods. In another study, Juslin and Laukka (2001) assessed the acoustic profile of five basic emotions (i.e., anger, disgust, fear, happiness, sadness). Analyses of variance (ANOVA) revealed significant differences between emotions on 15 acoustic parameters, including measures of F0, speech rate, voice quality, and spectral cues.

4.1.3. Decoding of emotions

Several studies have examined the ability to decode or recognise affective states based on vocal cues alone (see the following for reviews: Juslin & Laukka, 2003; Scherer et al., 2003). In a typical recognition paradigm, participants make judgments about emotions expressed in brief recordings of speech-embedded prosody produced by actors (El Ayadi et al., 2011; Scherer, 2003). Response options are typically provided in forced-choice format, where participants discriminate between emotion labels (Banse & Scherer, 1996; Juslin & Laukka, 2001; Laukka, 2005). One limitation of this approach is the use of simulated portrayals, which are not as ecologically valid as natural expressions (Scherer, 2003). For example, actors are likely to exaggerate more prototypical cues while missing more subtle ones (Scherer, 2003). It can be reasoned, however, that emotional expressions occurring in real-life are also "posed" to some extent, with pull factors (e.g., display rules) contributing to their portrayal (Banse & Scherer, 1996; Scherer et al., 2003).

Individuals can identify discrete emotions in speech prosody at accuracy rates of 43-65%, which are above chance levels (Banse & Scherer, 1996; Hawk et al., 2009; Juslin & Laukka, 2001; Scherer, 1986; Scherer, Banse, Wallbott, & Goldbeck, 1991). Individuals can also recognise emotional prosody from foreign cultures above chance, although accuracy is higher for members of the same cultural group (Elfenbein & Ambady, 2002; Juslin & Laukka, 2003;

Laukka et al., 2016; Pell, Paulmann, Dara, Alasseri, & Kotz, 2009; Scherer, Banse, & Wallbott, 2001; Van Bezooijen, Otto, & Heenan, 1983). There appears to be a consistent pattern of recognition accuracy for the basic emotions across cultures, with prosody for anger and sadness being the easiest to identify (Bryant & Barrett, 2008; Elfenbein & Ambady, 2002; Juslin & Laukka, 2003; Laukka, 2005; Pell et al., 2009; Scherer, 2003; Scherer et al., 2001), and disgust being the most difficult (Banse & Scherer, 1996; Hawk et al., 2009). Of note, the pattern of recognition accuracy for basic emotions in facial expressions is different, with higher accuracy rates for disgust and variants of happiness (e.g., elation, joy), and lower rates for anger (Bänziger, Grandjean, & Scherer, 2009; Elfenbein & Ambady, 2002; Hawk et al., 2009).

Acoustic features predict one's ability to recognise emotions in speech prosody (Banse & Scherer, 1996; Coutinho & Dibben, 2013; Gobl & Chasaide, 2003; Juslin & Laukka, 2001; Laukka, Neiberg, Forsell, Karlsson, & Elenius, 2011; Pell et al., 2009; Sobin & Alpert, 1999). For example, Banse and Scherer (1996) regressed responses from human judges on several acoustic features in speech prosody and found that 10 features (e.g., mean F0, mean energy, duration of voiced periods) accounted for a moderate proportion of variance across 11 out of the 14 emotions assessed. Among the emotions, associations were strongest for hot anger. Specifically, judges relied on high mean F0, F0 variation, and energy differences between low and high frequency bands to identify hot anger. Studies using signal-masking techniques and acoustic synthesis (e.g., manipulation/filtering of specific acoustic features in voice samples) have also reported an association between acoustic features (e.g., F0, intensity, tempo, voice quality) and emotion recognition accuracy (Gobl & Chasaide, 2003; Johnson, Emde, Scherer, & Klinnert, 1986; Scherer, Koivumaki, & Rosenthal, 1972). Further, acoustic features (e.g., F0, first formant frequency, high frequency energy, attack or time of voice onset) account for the variance in emotional intensity ratings of speech prosody (Juslin & Laukka, 2001).

4.2. Neural Correlates

4.2.1. Voice-selective regions

This section focuses on the neurobiological mechanisms underlying the decoding of vocal emotions, beginning with a description of the voice processing network more broadly. This network includes regions overlapping with the social brain. Voice-selective regions have been identified in the temporal lobe ("temporal voice areas"), specifically the STS (Belin & Zatorre, 2003; Belin, Zatorre, & Ahad, 2002; Belin, Zatorre, Lafaille, Ahad, & Pike, 2000; Fecteau, Armony, Joanette, & Belin, 2004; Pernet et al., 2015; von Kriegstein & Giraud, 2004), which is considered to be the voice modality's equivalent of the FFA for face perception (Kanwisher et al., 1997). Belin et al. (2000) first reported greater activity in the upper banks of the bilateral STS (Figure 4.2) when participants passively listened to linguistic and non-linguistic human voices compared to non-vocal sounds (e.g., nature or mechanical sounds, other human sounds like handclaps, white noise, scrambled voices). They also reported higher activity in the right versus left STS. Of note, the right STS is particularly sensitive to the paralinguistic aspects of speech (e.g., emotional prosody) and non-linguistic vocal sounds (e.g., throat clearing, laughter; Belin et al., 2002), and plays a key role in representing voice identity (Belin & Zatorre, 2003; von Kriegstein, Eger, Kleinschmidt, & Giraud, 2003).

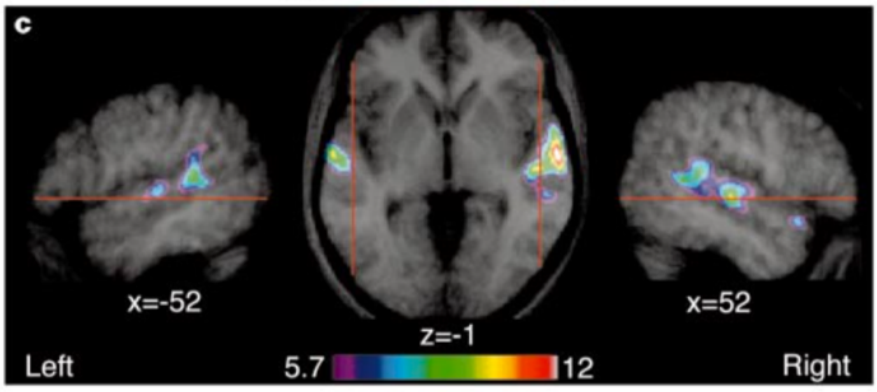


Figure 4.2. Voice-selective regions in the bilateral superior temporal sulci. Image source: Belin et al. (2000)

Studies have identified extra-temporal regions that are sensitive to human voices, including the bilateral IFG (Aglieri, Chaminade, Takerkart, & Belin, 2018; Andics et al., 2010; Fecteau, Armony, Joanette, & Belin, 2005; Pernet et al., 2015). Fecteau et al. (2005) reported that the left IFG (pars orbitalis/OFC) was more responsive to both linguistic and non-linguistic human voices compared to non-vocal sounds and non-human voices (e.g., animal calls). They reported that a homologous region in the right IFG was selective to non-linguistic human voices alone. Aglieri et al. (2018) identified "frontal voice areas" in the bilateral IFG (pars orbitalis, opercularis/OFC, and triangularis) and the precentral gyrus. They also reported increased functional connectivity between temporal and frontal voice areas, and found that higher connectivity between these regions correlated with higher performance on a voice recognition task administered out-of-scanner.

4.2.2. Emotional voice areas

Voice-selective regions in the STS and IFG are more responsive to linguistic and non-linguistic emotional voices compared to neutral ones (Beaucousin et al., 2007; Ethofer et al., 2006; Fecteau et al., 2005; Frühholz & Grandjean, 2013; Grandjean et al., 2005; Meyer, Zysset, von Cramon, & Alter, 2005; Wildgruber et al., 2004). The bilateral STG and MTG (adjacent to the STS) are also involved in emotional voice processing (Ethofer et al., 2012; Mitchell, Elliott, Barry, Cruttenden, & Woodruff, 2003; Morris, Scott, & Dolan, 1999). Of note, these temporal and frontal regions are not unique to emotional voice processing, and also serve other social cognitive functions like ToM, empathy, and face processing (Chapter 3).

Using a passive listening paradigm, Ethofer et al. (2012) localised "emotional voice areas" (regions responsive to emotional vs. neutral prosody) to the auditory cortices, specifically bilateral STG, Heschl's gyri, rolandic operculum, and the left MTG. They found that emotional

voice areas were functionally connected to the ipsilateral IFG, and to a lesser extent, the thalamus, occipital, parietal, and motor regions. Further, DTI was suggested to show strong structural connectivity between the emotional voice areas and ipsilateral IFG, IPL, and occipital cortex. Connectivity between emotional voice areas and frontoparietal regions could reflect the involvement of an "audio-motor loop" (similar to the concept of an auditory MNS; see Section 3.3.2), for action representation of the perceived vocal emotions. Connectivity with the occipital cortex could support cross-modal (visual) representations of the auditory stimuli.

Schirmer and Kotz (2006) proposed a multi-step, hierarchical model of emotional voice processing (Figure 4.3), which applies directly to speech-embedded prosody, although it may be adapted for non-linguistic emotional vocalisations (e.g., Bestelmeyer, Maurage, Rouger, Latinus, & Belin, 2014). There are three stages to this model, beginning with low-level sensory processing in the auditory cortex (Heschl's gyrus, rolandic operculum) where acoustic features of the voice are extracted. Information about acoustic features is then transferred laterally to the STG and STS (i.e., auditory "what" pathway), which integrate individual components into an "emotional gestalt". Cognitive judgments about the voice (e.g., emotion labelling tasks) are supported by the IFG, particularly the pars triangularis and pars orbitalis/OFC.

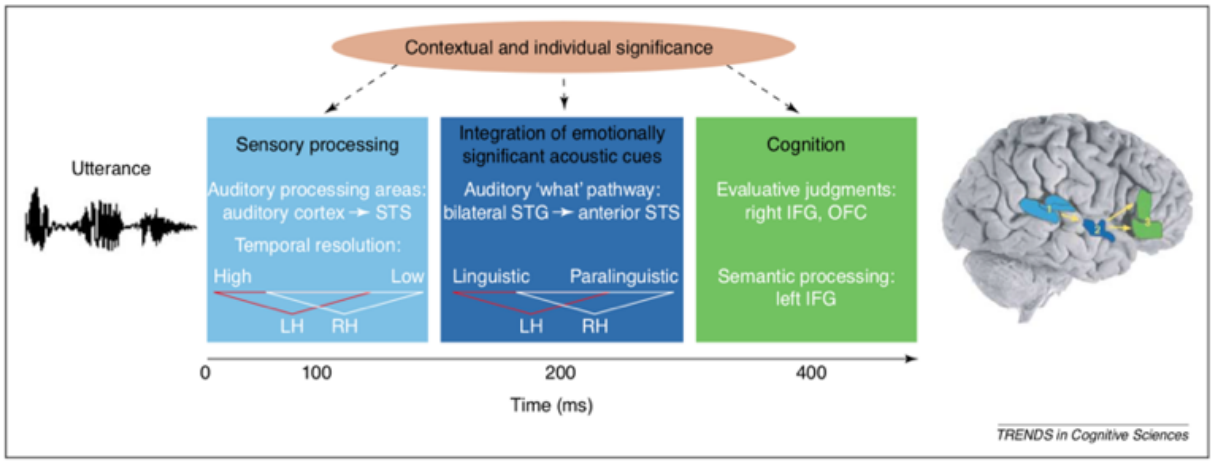


Figure 4.3. Hierarchical model of emotional voice processing proposed by Schirmer and Kotz (2006). This figure shows the hemisphere-specific roles and time course at each stage, and indicates that contextual and individual significance of the emotional voice may facilitate processing at any stage. Image source: Schirmer and Kotz (2006)

Schirmer and Kotz's (2006) model incorporates bilateral structures, but acknowledges that the left and right hemispheres have different roles in emotional voice processing. The left hemisphere is more specialised for processing the linguistic aspects of prosodic stimuli, while the right hemisphere is more specialised for processing paralinguistic cues. For example, the left auditory cortex has finer temporal resolution for rapidly changing information in speech, whereas the right auditory cortex has lower temporal resolution for pitch changes. The left STS/STG is sensitive to how "speech-like" the stimuli is, whereas the right STS/STG is less sensitive to speech intelligibility. The left IFG is responsible for integrating speech with emotional prosody, whereas the right IFG is involved with evaluating its emotional significance.

The bilateral amygdala and anterior insula are also involved in emotional voice processing (Beaucousin et al., 2007; Fecteau, Belin, Joanette, & Armony, 2007; Mitchell et al., 2003; Morris et al., 1999; Sander & Scheich, 2001, 2005). The amygdala is not just sensitive to

negative vocal emotions like fear and anger (Frühholz & Grandjean, 2013; Morris et al., 1999; Phillips et al., 1998; Scott et al., 1997), but also to positive vocal emotions like happiness and sexual pleasure (Fecteau et al., 2007; Sander & Scheich, 2001). Activation of the insula may reflect its general role in salience detection and awareness (Craig & Craig, 2009; Uddin, 2014), or in auditory processing more broadly (e.g., detection of novel sounds, allocation of auditory attention, temporal/phonological processing; Bamiou, Musiek, & Luxon, 2003).

4.3. Emotional Voice Processing in ASD

4.3.1. Deficits in emotional prosody recognition

Less ASD research has been conducted on emotion recognition in the vocal compared to facial modality. To date, no systematic review or meta-analysis has integrated findings exclusively across studies on vocal emotion recognition in ASD. A review by Lartseva, Dijkstra, and Buitelaar (2015) covered "emotional language processing" in ASD more broadly, including but not limited to the processing of emotional prosody. The majority of studies in their review pertained to the perception of emotional content in speech or written words (e.g., memory for emotion-laden words/sentences, use of emotion words in discourse). The authors concluded that individuals with ASD demonstrate deficits with emotional language processing, irrespective of sensory modality (e.g., auditory/visual), stimulus complexity (e.g., single words/sentences), task design (e.g., explicit/implicit), and one's level of language development.

Appendix C provides a summary of 30 behavioural studies that assessed the recognition of basic emotions in speech prosody in ASD. A substantially smaller number of studies (n = 11) that assessed the recognition of non-linguistic emotional voices (or "vocal affect bursts", as discussed in Section 4.4) are also included in the appendix. Studies were identified from a

recent search (January 2019) of the following terms (title/abstract) on the PsycINFO and PubMed databases: "autism", "voice" (or "vocal"), and "emotion". Information summarised in the appendix includes characteristics of the ASD and control groups, emotions assessed, stimuli and task design, and findings from group comparisons. Among the studies listed, most employed forced-choice labelling (e.g., select emotion category from a list of labels), cross-modal matching tasks (e.g., match emotional voice to the face), or a mix of both. Most studies also assessed individuals with HFA instead of individuals with comorbid intellectual disability. ASD and control groups were often matched on age and/or verbal ability. Table 4.2 lists the forced-choice labelling and cross-modal matching studies on basic emotional prosody recognition from Appendix C that reported: (i) lower performance in the ASD group relative to controls (ASD < Controls), or (ii) no significant group differences (ASD = Controls).

Table 4.2

Performance on Common Tasks Assessing Basic Emotional Prosody Recognition in High- and Low-Functioning Individuals with ASD Relative to Controls

Task	ASD < Controls[a]	ASD = Controls[b]
Forced-choice labelling		
HFA	• Macdonald et al. (1989) • Mazefsky and Oswald (2007) • Philip et al. (2010) • Heaton et al. (2012) • Globerson, Amir, Kishon-Rabin, and Golan (2015) • Fridenson-Hayo et al. (2016) • Matsumoto et al. (2016) • Chiew and Kjelgaard (2017) • Schelinski and von Kriegstein (2019)	• Baker, Montgomery, and Abramson (2010) • Brennand, Schepman, and Rodway (2011) • Jones et al. (2011) • Ketelaars et al. (2016)
LFA[c]	• Hobson, Ouston, and Lee (1989) • van Lancker, Cornelius, and Kreiman (1989)	• Gioia and Brosgole (1988) • Jones et al. (2011)

Task	ASD < Controls[a]	ASD = Controls[b]
Cross-modal matching		
HFA	• Lindner and Rosén (2006) • Kahana-Kalman and Goldman (2008) • Grossman and Tager-Flusberg (2012) • Le Sourn-Bissaoui, Aguert, Girard, Chevreuil, and Laval (2013) • Stewart, McAdam, Ota, Peppé, and Cleland (2013) • Taylor et al. (2015) • Wang and Tsao (2015)	
LFA[c]	• Loveland et al. (1995) • Golan, Gordon, Fichman, and Keinan (2018)	• Gioia and Brosgole (1988) • Hobson, Ouston, and Lee (1988)

Note. Refer to Appendix C for more details about each study. Only studies with control groups matched on age, IQ, and/or verbal abilities are listed here. HFA = high-functioning autism; LFA = low-functioning autism.

[a]Lower performance (recognition accuracy and/or reaction time) by ASD group compared to controls at $p < .05$, $p < .01$, or $p < .001$

[b]No significant differences between ASD and control groups ($p > .05$)

[c]Includes individuals with intellectual disability or described by the authors as having low verbal mental age/VIQ

Several studies ($n = 11$) showed that individuals with ASD (both high- and low-functioning) had lower performance than controls when identifying basic emotions in speech prosody on forced-choice labelling tasks (Table 4.2). Some studies also showed that despite poor performance on emotional task conditions, individuals with ASD demonstrated intact performance on control conditions (e.g., recognise object sounds or semantic content in speech; Hobson et al., 1989; van Lancker et al., 1989). This suggests that emotional voice processing deficits in affected individuals may occur independently of their general ability to attribute meaning to auditory stimuli.

Several studies (n = 9) also showed that individuals with ASD were poorer than controls at matching basic emotional prosody to facial expressions or body postures (Table 4.2). For example, one study showed that relative to controls, young children with ASD (3-4 years) demonstrated less preferential looking towards emotionally-congruent pairs of facial and vocal expressions (Kahana-Kalman & Goldman, 2008). Importantly, studies have shown that ASD and control groups perform similarly on control conditions that assess the matching of inanimate objects to neutral sounds (Hobson, 1986; Kahana-Kalman & Goldman, 2008; Loveland et al., 1995). This suggests that ASD deficits in cross-modal integration are not generalised across visual and auditory information, but specific to emotional expressions.

Despite substantial evidence for a deficit, a small number of studies have reported that individuals with ASD show intact recognition of basic emotions in speech prosody, at least on measures of recognition accuracy (Baker et al., 2010; Chiew & Kjelgaard, 2017; Jones et al., 2011; Ketelaars et al., 2016; Matsumoto et al., 2016; Tobe et al., 2016). However, individuals with ASD who demonstrate intact accuracy rates may be slower (reaction time) than controls at classifying emotional prosody, suggesting more subtle processing deficits (Ketelaars et al., 2016; Matsumoto et al., 2016). Further, deficits in ASD are more pronounced for the recognition of prosodic stimuli with low- versus high-intensity cues (Globerson et al., 2015; Grossman & Tager-Flusberg, 2012; Mazefsky & Oswald, 2007).

Individuals with ASD also have difficulty inferring complex emotions from speech prosody. This is reflected in their poor performance on standardised tasks assessing ToM from tone of voice, specifically the Reading the Mind in the Voice task (Golan et al., 2007; Rutherford et al., 2002) and the CAM Face-Voice Battery (Fridenson-Hayo et al., 2016; Golan, Baron-

Cohen, & Hill, 2006). In addition, they have difficulty recognising speech prosody that represents intentions or attitudes that differ from their literal meaning (e.g., "fooling", sarcasm; Horie & Okamura, 2017; Tobe et al., 2016). One study showed that individuals with ASD were slower than controls to infer mental states from speech prosody, although both groups had similar levels of recognition accuracy (Chevallier, Noveck, Happé, & Wilson, 2011).

4.3.2. Atypical brain function

Gervais et al. (2004) conducted the first fMRI study on general voice processing in ASD, and found that affected individuals failed to activate bilateral voice-selective regions (i.e., STS) in response to vocal sounds. In contrast, they showed normal patterns of brain activation to non-vocal sounds. Abrams et al. (2013) revealed that individuals with ASD showed reduced functional connectivity between bilateral voice-selective regions and the reward network (e.g., OFC, ventral tegmental areas, nucleus accumbens, insula, ventral mPFC) and amygdala. These findings suggest that individuals with ASD may perceive voices as being less meaningful, with little social relevance or reward value. The researchers also found that the strength of connectivity between the posterior STS and the reward network and amygdala correlated with levels of social communication deficits in ASD.

To date, only three fMRI studies have directly assessed the neurobiological correlates of emotional voice processing in ASD, all using emotional speech prosody (Eigsti et al., 2012; Gebauer et al., 2014; Rosenblau et al., 2017). Eigsti et al. (2012) measured brain activation to statements and questions spoken in an angry versus neutral tone. Participants were not instructed to attend to emotional prosody in speech, but were required to identify whether each sentence was about a living thing (implicit task). The ASD and control groups performed the task equally well, although group differences in brain activation were observed. Specifically,

the ASD group showed higher activation than controls in several bilateral or right-lateralised regions, including the social brain (e.g., mPFC, STG, TPJ), parahippocampal gyrus, precentral gyrus, and globus pallidus. The researchers reasoned that the ASD group was therefore less efficient at processing emotional prosody, requiring greater memory demands, visualisation, motor planning, language-relevant cognitive control, attention, and mentalising. The ASD group showed lower activation than controls in the left IFG alone, suggesting reduced integration of prosodic cues with speech or reduced social cognition (e.g., empathy). Of note, the authors reported that "a conservative threshold of $p < .001$ was used to account for multiple comparisons" (p. 606), although it is unclear if statistical corrections (e.g., family-wise error correction; false-discovery rate) were used to address the multiple comparison problem of fMRI analysis.

Gebauer et al. (2014) assessed brain activation in ASD and control groups using an explicit task, on which participants were required to rate the valence and intensity of emotional prosody in sentences along a scale from "very sad" to "neutral" to "very happy". The ASD group assigned lower intensity ratings for happy and sad prosody compared to controls, and demonstrated trends towards enhanced activation in the right caudate and decreased activation in the left precentral gyrus (results were reported at a voxel-wise uncorrected statistical threshold of $p < .001$). The authors suggested that the latter finding indicated reduced left-lateralisation of language processing in the ASD group. A trend for enhanced activation in the ASD group was also observed in the right middle/superior frontal gyrus and left superior parietal lobe for happy prosody, specifically. These findings are broadly consistent with those of Eigsti et al. (2012) and suggest increased attentional and executive demands for emotional voice processing in ASD.

Rosenblau et al. (2017) assessed emotional voice processing in ASD using both implicit (gender recognition) and explicit (emotion recognition) tasks in-scanner. They employed prosodic stimuli for basic and complex emotions in both tasks. The ASD group and control groups performed equally well on both tasks. Both groups activated bilateral emotional voice areas (e.g., STS, IFG) regardless of task design and the complexity of emotions. Direct group comparisons revealed no significant differences in brain activation for general emotional voice processing (basic and complex emotions combined). However, there was a significant group by complexity interaction, with the ASD group showing less activation than controls in emotional voice areas (e.g., bilateral STS, STG, insula, right amygdala) for "complex versus basic" emotions. The authors did not report whether group differences in brain activation were found for basic emotions alone (i.e., basic emotions vs. neutral prosody).

Other fMRI studies have reported that individuals with ASD demonstrate atypical brain activation when making judgments about mental states (e.g., speaker's intentions, irony) in speech-embedded prosody (Wang, Lee, Sigman, & Dapretto, 2007; Wang, Lee, Sigman, & Dapretto, 2006). Wang et al. (2006) reported that individuals with ASD showed higher activation than controls in emotional voice areas and other social brain regions (e.g., left STS, right temporal pole, right IFG) when deciphering whether a speaker was being sincere or sarcastic from prosodic cues alone, or when integrating prosodic cues with contextual information. These findings suggest that individuals with ASD require additional cognitive resources to discern mental states in the voice. In another study, Wang et al. (2007) assessed brain activation associated with the detection of irony in cartoon drawings (containing facial expressions) that were presented with audio recordings of sincere or ironic remarks. They found that the ASD group showed lower activation in the mPFC relative to controls. However, activation of the mPFC increased in the ASD group when they were instructed to attend to tone

of voice or facial expressions alone. This suggests that "attentional training" may modulate social brain function and facilitate the understanding of mental states in the voice in individuals with ASD.

4.3.3. Expression in the BAP

Research on emotional voice processing in the BAP is scarce. Two behavioural studies have assessed the recognition of emotional prosody in relatives of individuals with ASD. One study found that siblings of children with comorbid ASD and ADHD were worse than controls, but better than the affected children themselves, at identifying basic emotions in speech-embedded prosody and faces (Oerlemans et al., 2014). However, it is impossible to ascertain the relative contributions of ASD- versus ADHD-specific factors on reduced performance in the sibling group compared to controls. Replication of these findings in a sample of relatives of autistic individuals without a comorbid diagnosis of ADHD will provide stronger evidence for poor recognition of emotional speech prosody in the BAP Another study found that parents of children with ASD were worse than controls at identifying complex emotions in speech prosody on the Reading the Mind in the Voice task, although they did not show any deficits on the equivalent Eyes Task (Tajmirriyahi et al., 2013).

One study examined the neural correlates of emotional prosody processing in the BAP using electrophysiological measures (Korpilahti et al., 2007). Compared to controls, boys with ASD and their fathers demonstrated atypical auditory ERP responses (e.g., slower processing of voices), particularly over the right-hemisphere, while listening to changes in F0 indicating tender and angry prosody. These findings suggest that right-hemisphere dominance for emotional voice processing may be compromised in the BAP, although replication and

evidence from neuroimaging studies are required to determine more precise regions of atypical activity.

There is currently no evidence for an association between reduced emotional voice processing and BAP traits in the general population. Specifically, Ingersoll (2010) found that scores on the AQ correlated with the recognition of facial emotions, but not emotional prosody, in undergraduate students. Ingersoll reasoned that this discrepancy could be accounted for by the fact that emotions were significantly easier to recognise in the face compared to the voice. Ingersoll suggested that further research is required to identify modality-specific mechanisms of emotion processing in the BAP.

4.4. Vocal Affect Bursts

4.4.1. Alternative stimuli for emotion research

The studies reviewed in this chapter primarily pertain to the processing of emotional speech prosody, with less attention given to non-linguistic vocal expressions of emotion. The latter are also known as vocal forms of "affect bursts", a term introduced by Scherer (1994) to describe "brief, discrete expressions of affect in both face and voice as triggered by clearly identifiable events" (p.170). Scherer (1994) proposed that facial and vocal affect bursts can be classified along a dimension of conventionality (Figure 4.4), which reflects the relative contribution of push and pull effects on the expression. Push effects refer to the "externalisation of naturally occurring internal processes" (e.g., physiological arousal), while pull effects refer to "socioculturally determined norms for the communication of internal states and behavioural intentions" (p.166, Scherer, 1994).

Scherer labelled affect bursts which are less conventionalised (i.e., more push versus pull effects) as "raw expressions" and those that are more conventionalised (i.e., more pull versus push effects) as "affect emblems" (Figure 4.4). Within the voice domain, raw expressions include non-linguistic vocalisations that occur reflexively with physiological changes which accompany the affective state, such as laughter, cries, screams, growls, and gasps. In contrast, affect emblems are more subject to voluntary control and include affective interjections with a constant phonemic structure (e.g., "wow!", "ouch!", and "yuck!"), although these are distinct from linguistic interjections that can take on other meanings in a non-emotional context (e.g., "heaven!", "no!"; Schröder, 2003).

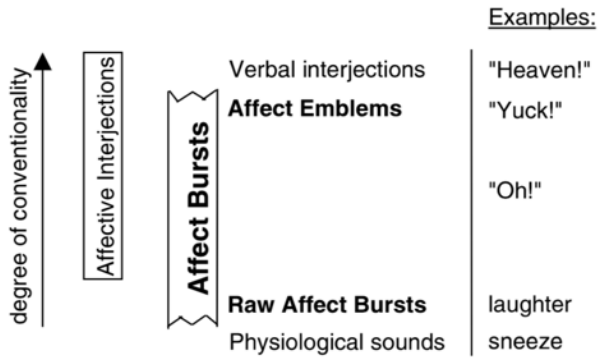


Figure 4.4. Classification of vocal affect bursts along a dimension of conventionality. Vocalisations on the lower end of the dimension are influenced by more push versus pull effects, whereas those on the higher end are influenced by more pull versus push effects. Image source: Schröder (2003)

This thesis focuses on raw expressions of non-linguistic vocalisations, hereafter simply referred to as "vocal affect bursts", as per Scherer's (1994) preferred terminology for emotional expressions on the "extreme push pole" (p.183) of the dimension. Given the relative pureness of their emotional cues, vocal affect bursts—particularly those conveying basic emotions—are considered to be less culturally-dependent than emotional speech prosody, and hence, appropriate for cross-cultural research on emotional voice processing (Belin, Fillion-Bilodeau, & Gosselin, 2008; Cordaro, Keltner, Tshering, Wangchuk, & Flynn, 2016; Kersken, Zuberbühler, & Gomez, 2017; Laukka et al., 2013; Sauter, Eisner, Ekman, & Scott, 2010).

One cross-cultural study found that vocal affect bursts of basic emotions (e.g., anger, disgust, fear, joy, sadness, surprise) produced by British English speakers and members of an isolated Namibian tribe were well recognised across listeners from both cultures (Sauter, Eisner, Ekman, et al., 2010). In contrast, the authors found that vocal affect bursts of emotions not typically considered "basic" (e.g., achievement/triumph, relief, sensual pleasure) were less recognisable between cultures, although listeners could accurately identify most of the emotions expressed by their own culture group.

Vocal affect bursts are also considered to be precursors of emotional prosody (e.g., acquired earlier than speech) and have strong evolutionary roots, showing phylogenetic continuity with vocalisations from other mammalian species (Belin, Fecteau, et al., 2008; Filippi, 2016; Frühholz & Grandjean, 2013; Seyfarth & Cheney, 2017). For example, the perception of emotional animal vocalisations has been found to activate similar regions as human vocal affect bursts in the human brain, particularly the right OFC (Belin, Fecteau, et al., 2008). One study also found that despite their phylogenetic distance, humans and dogs show activation in similar anterior temporal regions (e.g., temporal pole) when listening to species-specific nonverbal emotional vocalisations (Andics, Gácsi, Faragó, Kis, & Miklósi, 2014).

Unlike emotional speech prosody, acoustic cues in vocal affect bursts are not constrained to the segmental and prosodic structure of language, and have more capacity to vary, with less precise movement of the articulators (Sauter, Eisner, Ekman, et al., 2010; Scott, Sauter, & McGettigan, 2010). They are instead shaped by "roughly positioned pharyngeal/oral/labial constrictions" (p.187), which vary with the accompanying facial expression (Scott et al., 2010). A small number of studies have assessed the encoding of vocal affect bursts. Patel, Scherer, Björkner, and Sundberg (2011) examined whether acoustic parameters can be useful for

distinguishing between discrete emotions (e.g., relief, sadness, joy, panic fear, hot anger) in vocal affect bursts. They found that mean F0, equivalent sound level, and several measures of voice quality (e.g., jitter, shimmer, harmonic-to-noise ratio, pulse amplitude, maximum glottal flow declination rate, alpha ratio) were useful for distinguishing between at least one pair of emotions. A principal components analysis of their data also revealed that vocal affect bursts can be differentiated along three dimensions: (i) phonatory effort (i.e., subglottal pressure influenced by rate/breadth of respiration, reflecting emotional arousal), (ii) perturbation (i.e., hypo- or hypertension of glottal adduction, reflecting the degree of power to cope with a situation), and (iii) frequency. Consistent with research on emotional speech prosody, the authors also found little evidence for acoustic markers of valence in vocal affect bursts.

In another study, Sauter, Eisner, Calder, and Scott (2010) found that a combination of amplitude, pitch, and spectral information in non-linguistic emotional vocalisations were sufficient for distinguishing different categories of emotions (e.g., achievement/triumph, amusement, anger, contentment, disgust, sensual pleasure, relief, sadness, and surprise; except for fear, which was only predicted by spectral information). The authors preferred to refer to these stimuli as "non-verbal vocal expressions of emotion" instead of vocal affect bursts, to avoid the connotation of brevity in "burst" terminology. They found that nine out of ten emotions (all but surprise) were predicted by variance in spectral information, whereas only four emotions were predicted by pitch cues (e.g., surprise, achievement, anger, relief). As such, variance in spectral information appeared to be equally or more important than pitch cues for predicting emotions in non-verbal vocal expressions. Low and high spectral variance also predicted ratings for negative and positive emotions, respectively. Collectively, acoustic measures accounted for approximately 60% of perceived arousal of the stimuli, whereas they only accounted for 17% of perceived valence.

Decoding studies have reported that vocal affect bursts are identified at high accuracy rates, ranging from 63-90%, averaged across the emotions assessed per study (Belin, Fillion-Bilodeau, et al., 2008; Hawk et al., 2009; Lima, Anikin, Monteiro, Scott, & Castro, 2018; Sauter, Eisner, Calder, et al., 2010; Sauter, Panattoni, & Happé, 2013; Schröder, 2003). These studies assessed a mix of the basic emotions and other affective states (e.g., sensual pleasure, relief, admiration, contempt, embarrassment, contentment, boredom, threat, worry, achievement/triumph, pride, pain), with variability in recognition accuracy rates observed between emotions. Some studies also included a mix of raw expressions and affect emblems (assessed together), with the latter being more conventionalised and hence, partly accounting for the high mean accuracy rates reported (Hawk et al., 2009; Schröder, 2003). Of note, studies comparing modalities of emotional vocal expression have found that vocal affect bursts are easier to identify than speech prosody, suggesting that they provide more discriminable information about affective states (Hawk et al., 2009; Heaton et al., 2012; Sauter et al., 2013). One study also reported high automaticity in the recognition of vocal affect bursts, with stimuli classified at high accuracy (90%) within 500ms of exposure, even under increasing attentional demands (Lima et al., 2018).

As alluded to earlier, vocal affect bursts have minimal associations with language and may thus present an advantage over speech prosody for research on emotional voice processing. Emotional meaning in vocal affect bursts is carried by the segmental structure of the voice alone, whereas emotional meaning in speech prosody is carried by the syntactic structure and semantic content of speech. Further, unlike emotional prosody, vocal affect bursts are not subjected to interactions with linguistic prosody. Linguistic prosody serves grammatical and pragmatic functions in speech, like identifying contrastive word stress (focus) or differentiating between declarative (statement) versus interrogative (question) sentences (Cutler, Dahan, &

van Donselaar, 1997; Wagner & Watson, 2010). While emotional and linguistic prosody are functionally distinct, their boundaries are difficult to define, as they depend on similar acoustic cues like variations in F0, amplitude, and voice quality (Belyk & Brown, 2014; Karpiński, 2012). Acoustic cues in emotional prosody can also vary with modifications to linguistic prosody. For example, Pell (2001) reported little variation in F0 across emotion categories (e.g., happiness, sadness, anger, neutral) when speakers were asked to integrate emotional prosody with contrastive word stress while producing interrogative sentences, whereas emotion-related distinctions in F0 were found for declarative sentences. Of note, distinct brain regions are associated with the evaluation of emotional (e.g., bilateral OFC) and linguistic (e.g., left IFG) prosody in speech, although both forms of prosody also share overlapping activation in the right dorsolateral cortex (Wildgruber et al., 2004).

4.4.2. Application to ASD and the BAP

Overall, the relative pureness of emotional cues in vocal affect bursts suggests that they are suitable alternatives for research targeting the behavioural and neuroimaging markers of emotional voice processing in ASD and the BAP. As noted, the majority of studies on emotional voice processing in ASD have assessed the recognition of emotional speech prosody, which requires the concurrent decoding of emotional and linguistic cues. Therefore, poor performance on tasks of emotional prosody recognition may not only reflect reduced social cognition in ASD, but also the confounds of reduced linguistic prosody recognition and verbal abilities more broadly (e.g., Diehl, Bennetto, Watson, Gunlogson, & McDonough, 2008; Järvinen-Pasley, Peppé, King-Smith, & Heaton, 2008; McCann & Peppé, 2003; McCann, Peppé, Gibbon, O'Hare, & Rutherford, 2007).

Other factors like executive function may also influence emotional prosody recognition in ASD, as participants must disregard linguistic information and selectively attend to the

speaker's tone of voice to decipher emotional cues in speech (Heaton et al., 2012). Consistent with this view, one study showed that emotional prosody recognition in ASD correlated positively with lower executive functions like divided attention, working memory/sequencing, set-shifting, and inhibition (Filipe, Frota, & Vicente, 2018). It is therefore possible that atypical brain function related to emotional prosody recognition in ASD (e.g., Eigsti et al., 2012; Gebauer et al., 2014) at least partially reflects the increased cognitive demands of disambiguating emotional cues from linguistic components in speech.

A small number of behavioural studies (n = 11) have utilised vocal affect bursts to assess emotional voice processing in ASD (Table 4.3; see also Appendix C). Vocal affect bursts from each study were raw expressions (i.e., not affect emblems) of all six basic emotions or a subset of these emotions. As shown in Table 4.3, findings across studies are mixed, although the majority (n = 7) reported poorer recognition of vocal affect bursts for individuals with ASD compared to controls across different types of tasks. The studies cited here assessed performance in both high-functioning individuals and those with lower intellectual function, characterised primarily by low verbal or non-verbal mental age. Most of these studies employed control groups that were matched to the ASD groups on mean chronological age, mental age (verbal or non-verbal), and/or IQ.

Table 4.3

Performance on Tasks Assessing Vocal Affect Burst Recognition in High- and Low-Functioning Individuals with ASD Relative to Controls

Task	ASD < Controls[a]	ASD = Controls[b]
Forced-choice labelling		
HFA	• Heaton et al. (2012) • Charbonneau et al. (2013)[c]	• Jones et al. (2011) • Xavier et al. (2015)[c]
LFA[d]		• Jones et al. (2011)
Free-choice labelling		
LFA	• Hobson et al. (1989)	
Cross-modal matching		
LFA[d]	• Hobson (1986) • Ozonoff et al. (1990) • Golan et al. (2018)	• Hobson et al. (1988) • Prior, Dahlstrom, and Squires (1990)
Congruence (same/different)		
HFA	• Vannetzel et al. (2011)[c]	

Note. Refer to Appendix C for specific details about each study. Only studies with control groups matched on age, IQ, and/or verbal and non-verbal abilities are listed here. HFA = high-functioning autism; LFA = low-functioning autism.

[a]Lower performance (recognition accuracy) by ASD group relative to controls at $p < .05$, $p < .01$, or $p < .001$

[b]No significant differences between ASD and control groups ($p > .05$)

[c]Study required participants to make judgments about both unimodal (voice only) and cross-modal (voice-face pairs) stimuli

[d]Participants had intellectual disability or low verbal/non-verbal mental age

Early studies of general emotion perception in ASD primarily employed cross-modal matching tasks, in which children with lower intellectual function were required to match drawings or photographs of emotional facial expressions to vocal affect bursts, among other forms of emotional expressions like gestures and situational contexts (Hobson, 1986; Hobson et al., 1988; Ozonoff et al., 1990; Prior et al., 1990). These studies also included non-emotional

control tasks, where participants were required to match emotionally neutral drawings or photographs of objects and events to neutral non-human sounds (e.g., train in motion, dog barking, car starting, bird singing). Hobson (1986) reported that children with ASD performed more poorly than controls matched on verbal and performance IQ when assigning facial expressions to vocal affect bursts. In contrast, no group differences were found for the control task, suggesting an emotion-specific deficit in multisensory processing. Ozonoff et al. (1990) also reported poorer matching of faces to vocal affect bursts in children with ASD when they were compared to controls matched on non-verbal mental age. However, unlike Hobson (1986), they found that poor ASD performance also extended to the non-emotional task, and concluded that emotion processing was not likely to be a primary deficit in ASD. Other early studies reported no group differences on both emotional and non-emotional cross-modal matching tasks when children with ASD were compared to controls matched on verbal mental age (Hobson et al., 1988; Ozonoff et al., 1990; Prior et al., 1990).

A more recent study assessed the matching of emotional facial expressions to vocal affect bursts, emotional word labels, and other emotional faces in ASD children with lower intellectual function (Golan et al., 2018). The authors reported poorer performance for all three conditions in the ASD group compared to controls matched on verbal mental age. Within the ASD group, participants performed better on the cross-modal voice-face (and word-face) condition compared to the unimodal face-face condition. This suggests that emotional cues in non-linguistic vocal expressions (and verbal content in written words) can facilitate the recognition of emotional faces in ASD, as vocal affect bursts often accompany changes in facial expressions. On another note, the authors reported that the voice-face condition was the only significant predictor of communication (e.g., receptive and expressive language, reading, writing) on a teacher-report measure of adaptive functioning for the ASD group, suggesting

that difficulties with multisensory emotional processing may influence their ability to effectively exchange information with others in real-life settings.

Studies have also utilised unimodal (voice only) tasks to assess the recognition of vocal affect bursts in ASD. Unlike cross-modal matching tasks, these paradigms allow a more direct assessment of emotional voice processing by excluding the influence of multisensory integration on task performance. Like cross-modal matching tasks, however, these paradigms have also yielded inconsistent findings, with some reporting an deficit in ASD (Charbonneau et al., 2013; Heaton et al., 2012; Hobson et al., 1989; Vannetzel et al., 2011) and others reporting no deficit (Jones et al., 2011; Xavier et al., 2015). Heaton et al. (2012) reported that participants with HFA were worse than age- and IQ-matched controls at labelling emotions in vocal affect bursts and emotional speech prosody. The authors also reported that levels of alexithymia correlated with performance across modalities within each group. Of note, supplementary analyses revealed that the HFA and control groups demonstrated better accuracy for vocal affect bursts compared to emotional speech prosody, supporting evidence for higher discriminability of non-linguistic vocal expressions. However, this discrepancy in performance between modalities was greater for the HFA group, which suggests that less complex forms of vocal expressions facilitated emotional voice processing to a greater extent in individuals with HFA compared to controls.

In another forced-choice labelling study, Jones et al. (2011) examined general emotion recognition ability for vocal affect bursts and emotional speech prosody (plus facial expressions) in adolescents with ASD. Unlike Heaton et al. (2012), they found no differences between the ASD and control groups on total recognition accuracy for each modality. Instead, they found that IQ had a significant effect on performance, where participants (irrespective of

diagnostic group) with a higher FSIQ (≥80) were better at identifying emotions in each modality than participants with a lower FSIQ (≤80). Xavier et al. (2015) also found that children with HFA and controls labelled emotions in vocal affect bursts equally well, but reported that accuracy rates in each group correlated positively with chronological age. Age-related improvements in the HFA group could suggest that older participants were more efficient at applying compensatory strategies for emotional voice processing, although the authors did not explore this assumption further.

One study reported that children with PDD-NOS showed poor recognition of vocal affect bursts on an emotional congruence task, on which they were required to judge whether pairs of voices were the same or different. They were particularly worse than controls at judging congruence between voice pairs for anger and a neutral category. They also demonstrated difficulties with judging the emotional congruence of cross-modal voice-face pairs and unimodal face-face pairs that included a stimulus from the neutral category. The authors concluded that the PDD-NOS group tended to overattribute emotional states to neutral non-linguistic voices and faces, as consistent with a study by Eack et al. (2015) which reported that individuals with HFA had difficulty distinguishing between neutral and emotional facial expressions (see Section 3.4.2).

Within the neuroimaging literature on ASD, one pilot study incorporated non-linguistic stimuli of positive and negative valence (exact form of stimuli and their emotional categories were not specified) into an fMRI task to assess brain activity underlying the multisensory integration of emotional voice-face pairs in adolescents with HFA (Loveland, Steinberg, Pearson, Mansour, & Reddoch, 2008). Behavioural findings revealed no significant differences in performance accuracy and reaction time between the HFA group and age-matched controls when they

judged emotional congruence (same/different) between the cross-modal pairs. Despite this, the fMRI data revealed that the HFA group demonstrated less activity than controls in social brain regions (e.g., OFC, STG, PCC), the parahippocampal gyrus, and visual areas, suggesting compromised function of networks serving the integration of emotional auditory and visual stimuli in ASD. To date, however, no fMRI study has employed a unimodal task to directly assess the neural correlates of vocal affect burst recognition in ASD independent of the simultaneous processing of emotional faces.

Regarding the BAP, no behavioural study has utilised vocal affect bursts to assess emotional voice processing in family members of individuals with ASD. One fMRI study assessed brain activation to vocal affect bursts of laughter and cries in infant siblings (4-7 months) of individuals with ASD. They found that ASD siblings showed lower activation than controls in the right fusiform gyrus and left hippocampus when listening to cries, specifically. Unlike controls, these siblings also showed no voice selectivity in the STG and MTG when neutral voices were compared to non-vocal sounds. It is unclear, however, whether these findings indicate early markers of atypical voice processing in ASD instead of the BAP, since approximately 20% of infant siblings eventually display the full ASD phenotype in early childhood (Georgiades et al., 2013). Research on older relatives above the age of three years is therefore required to ascertain the integrity of brain function underlying vocal affect burst recognition in the BAP.

In summary, examining the brain and behavioural correlates of vocal affect burst recognition in ASD and the BAP is crucial for advancing our knowledge about auditory-related social cognition and social brain function in these populations. Identifying similarities/differences in the neurobiological mechanisms and behavioural profiles between groups will allow potential

endophenotypes of emotional voice processing to be identified. Research on vocal affect burst recognition should also be extended to the BAP in the general population, in order to fully characterise emotional voice processing abilities across the clinical spectrum of ASD and its broader phenotype.

4.5. Thesis Aims and Hypotheses

The primary objective of this thesis was to examine behavioural and brain correlates of emotional voice processing in ASD and the BAP using vocal affect bursts. More specifically, it aimed to characterise emotional voice processing abilities in: (i) ASD, (ii) the BAP in relatives, and (iii) the distribution of BAP traits in the general population. It also aimed to determine the neurobiological substrates underlying emotional voice processing in ASD and the BAP in relatives compared to healthy controls. Three studies were conducted to address these aims, each using the same purpose-built, web-based task to assess behavioural performance and/or an fMRI task (modified version of the web-based task) to elicit brain activation.

Study 1: Behavioural and brain correlates of emotional voice processing in ASD

The first study examined behavioural performance and brain function related to the recognition of vocal affect bursts in adolescents and adults with high-functioning ASD compared to typically-developing controls matched on age, sex, and IQ. Participants also rated the emotional intensity of vocal affect bursts using the web-based task. The following hypotheses were tested:

- **H_1**: The ASD group would show poorer ability to classify vocal affect bursts than controls, indicative of a vocal emotion recognition deficit

- **H_2:** The ASD group would show atypical brain activation for emotional voice processing relative to controls

Study 2: Behavioural and brain correlates of emotional voice processing in the BAP in relatives

The second study employed the same measures as Study 1 to assess adult family members of individuals with ASD and typically-developing controls without a family history of ASD, matched on age, sex, and IQ. Participants also rated the emotional intensity of vocal affect bursts using the web-based task. The family group was pre-determined to meet categorical criteria for the BAP on clinical assessment (i.e., BAP-positive status). The following hypotheses were tested:

- **H_1**: The BAP group would show poorer ability to classify vocal affect bursts relative to controls
- **H_2:** The BAP group would show atypical brain activation for emotional voice processing relative to controls

Study 3: Emotional voice processing and BAP traits in the general population

The third study employed the web-based task alone. It examined the relationship between the recognition of vocal affect bursts and self-ratings of BAP traits (on the BAPQ) in adults from the general population who reported no family history of ASD. Participants also rated the emotional intensity of vocal affect bursts using the web-based task. The following hypotheses were tested:

- **H_1**: Higher self-ratings of BAP traits for aloof personality, pragmatic language difficulties, and rigidity would correlate with poorer ability to classify vocal affect bursts

- **H_2**: Higher self-ratings of BAP traits (from the three domains) would also correlate with lower emotional intensity ratings for vocal affect bursts

CHAPTER 5

Study 1: Behavioural and Brain Correlates of Emotional Voice Processing in ASD

Overview: Study 1 used behavioural and fMRI measures to examine the recognition of vocal affect bursts and their neurobiological substrates in high-functioning individuals with ASD relative to controls. It was hypothesised that individuals with ASD would show a vocal emotion recognition deficit on a web-based (pre-scan) behavioural task relative to controls. It was also hypothesised that they would demonstrate atypical brain activation relative to controls when classifying emotions on a modified version of this task in-scanner. The premise of this study is summarised in a brief introductory section, which includes relevant research from the literature review.

5.1. Introduction

Social communication deficits are primary features of ASD. Specific characteristics include poor pragmatic language, reduced theory of mind, and difficulties expressing emotions or inferring the emotional states of others (Baron-Cohen, 2000; Harms et al., 2010; Volden, Coolican, Garon, White, & Bryson, 2009). Emotion research has focused on the recognition of facial expressions in ASD, with a recent meta-analysis of behavioural studies revealing significant impairment (Uljarevic & Hamilton, 2013). Attention has also been given to the recognition of emotional vocalisations in ASD, although research in this domain is less extensive.

Vocal emotion recognition in ASD has been primarily assessed using speech stimuli varying in emotional prosody (McCann & Peppé, 2003). The majority of such studies have reported poorer recognition of emotional speech prosody in individuals with ASD (including those who are high-functioning) compared to age- and IQ-matched controls, regardless of task type (e.g., forced-choice labelling or cross-modal matching) or whether the stimuli represented basic or complex emotions (Fridenson-Hayo et al., 2016; Grossman & Tager-Flusberg, 2012; Lindner & Rosén, 2006; Macdonald et al., 1989; see Table 4.2 for a more complete list). Among the neuroimaging literature, one fMRI study reported that relative to controls, individuals with ASD showed a significant decrease in activation in the superior temporal sulcus (STS), insula, and amygdala for processing complex emotions in speech prosody (Rosenblau et al., 2017). Other fMRI studies assessing the processing of basic emotions in speech prosody have reported findings suggesting a trend in ASD groups towards increased brain activation (i.e., at uncorrected significance thresholds) in regions that serve motor planning, social cognition, attention, cognitive control, and memory (e.g., precentral gyrus, medial frontal gyrus, superior temporal gyrus or STG, parahippocampal gyrus, precentral gyrus, basal ganglia), leading the

authors to suggest increased cognitive effort for emotional voice processing (Eigsti et al., 2012; Gebauer et al., 2014).

In addition to linguistic vocalisations, ASD deficits have been observed for the recognition of vocal affect bursts (e.g., laughter, cries, shrieks, gasps), a form of non-linguistic vocal expression (Charbonneau et al., 2013; Heaton et al., 2012; Vannetzel et al., 2011; see Section 4.4). Although sparse, studies on vocal affect bursts provide valuable insights into emotion processing abilities per se, in the absence of higher-order processing of linguistic and semantic components of prosodic speech. Vocal affect bursts are less conventionalised than emotional speech prosody, since they are influenced by more "push" (e.g., internal physiological factors) versus "pull" effects (e.g., sociocultural norms; Scherer, 1994; Schröder, 2003). They have evolutionary significance, sharing similarities to animal vocalisations (e.g., distress calls; Panksepp, 2005), and are considered precursors to emotional prosody in speech (Frühholz & Grandjean, 2013). They are also generally easier to identify than emotional speech prosody and may be more effective at eliciting the attention of others (Hawk et al., 2009).

The relative pureness of emotional signals conveyed by vocal affect bursts means they are well suited for studies examining the neurobiology of emotional voice processing in ASD. Vocal affect bursts have been incorporated into an fMRI study on cross-modal emotion perception in ASD (Loveland et al., 2008), which showed reduced activation relative to controls in regions serving social cognition, memory, and visual processing (e.g., OFC, STG, parahippocampal gyrus, posterior cingulate cortex, occipital structures). To date, however, no fMRI study has directly examined the recognition of vocal affect bursts in ASD using a unimodal paradigm where participants make explicit judgements about emotional states from vocal cues alone.

Such a paradigm avoids the complexity of emotional face processing and removes the confound of language implicit in fMRI studies of emotional prosody perception.

The present study examined the recognition of vocal affect bursts and their neurobiological correlates in high-functioning individuals with ASD and typically-developing controls matched for sex, age, and IQ. Prior to the fMRI scan, a seven-alternative forced-choice discrimination task was used to assess classification accuracy for vocal affect bursts corresponding to the six basic emotions (i.e., anger, disgust, fear, happiness, sadness, surprise) and a neutral category. Participants were also required to rate the intensity of each emotion in the pre-scan task. Whole-brain activation associated with the classification of vocal affect bursts was elicited using a simpler, two-alternative forced-choice fMRI discrimination task. It was hypothesised that compared to controls, the ASD group would show (i) poorer behavioural performance on the pre-scan task, and (ii) atypical brain activation (i.e., either increased or decreased relative to controls) on the fMRI task. Further, secondary analyses were performed to explore the link between informant-ratings of symptom severity in the ASD group and activation in regions associated with emotional voice processing, specifically the bilateral inferior frontal gyrus (IFG) and STS with adjacent middle and superior temporal gyri (Ethofer et al., 2012; Schirmer & Kotz, 2006; see also Section 4.2.2).

5.2. Method

This project was approved by the Human Research Ethics Committee (HREC) at The Royal Children's Hospital Melbourne and the Human Research Ethics Advisory Group at The University of Melbourne. All participants, or their parents in the case of minors, provided written informed consent.

5.2.1. Participants

Sixteen participants with ASD (12 males) were recruited from the Collaborative Autism Study (CATS) database at The Royal Children's Hospital and The University of Melbourne (HREC #25043). Participants were aged 13 to 51 years (M = 23.00, SD = 10.20). All were high-functioning (i.e., cognitively able), with a Full-Scale IQ in the *Average* to *Superior* range (94 – 134; M = 112.56, SD = 13.02) on the Wechsler Abbreviated Scale of Intelligence (WASI or WASI-II, depending on the year in which they were recruited to the CATS; Wechsler, 1999; Wechsler, 2011). Demographic information is summarised in Table 5.1. All participants had a community-based/clinical diagnosis of ASD based on DSM-IV or DSM-5 criteria (American Psychiatric Association, 2000, 2013) according to expert clinical evaluation, the Autism Diagnostic Interview-Revised (Lord, Rutter, & Couteur, 1994), Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1999), or the Childhood Autism Rating Scale (CARS; Schopler et al., 1988). Participants were re-assessed with an age-appropriate module (i.e., Module 4) from the ADOS-2 (Lord et al., 2012) to confirm their diagnosis (Table 5.1). Informant-report versions of the Social Responsiveness Scale-Second Edition (SRS-2; Constantino & Gruber, 2012) were also given to the participant's parent or another family member to measure the severity of ASD symptoms (Table 5.2). Eight participants reported psychiatric comorbidities (i.e., depression, anxiety, ADHD) and were on medical therapy. None reported a history of neurological disorders (e.g., epilepsy, traumatic brain injury).

A control group of 16 typically-developing participants was recruited from the community. Controls were matched on sex, age, and IQ (Table 5.1), and reported having no family history of ASD, with the exception of one who had a second-degree relative with ASD. Controls were screened for subclinical ASD traits (i.e., BAP) using the Broad Autism Phenotype Questionnaire (BAPQ; Hurley et al., 2007). None met BAP criteria on any BAPQ scale (i.e.,

total score, aloofness, pragmatic language difficulties, rigidity) according to norms developed for the general population (Sasson, Lam, et al., 2013). None reported a history of psychiatric or neurological disorders.

Table 5.1

Demographics for the ASD and Control Groups

	ASD (n = 16)	Controls (n = 16)
Sample Size (n)		
Males	12	12
Age in years		
M (SD)	23.00 (10.20)	23.19 (9.71)
Range	13-51	13-47
Full-Scale IQ		
M (SD)	112.56 (13.01)	116.88 (8.72)
Range	94-134	100-135
Verbal IQ		
M (SD)	112.81 (12.95)	117.25 (9.84)
Range	84-132	106-135
Performance IQ		
M (SD)	109.44 (16.12)	114.81 (9.40)
Range	74-134	99-129
Handedness (n)		
Right	12	16
ADOS-2 Severity Score[a]		
M (SD)	7.35 (1.87)	-
Severity Level	Moderate	-
Range	2 – 10[b]	

Note. Independent samples t-tests revealed no significant group differences for age, Full-Scale IQ, Verbal IQ, and Performance IQ ($p > .05$). *M* = mean; *SD* = standard deviation.

[a] Standardised severity scores were based on revised diagnostic algorithms for Module 4 of the ADOS-2 (Hus & Lord, 2014).

[b] One participant scored below cut-off for ASD on the ADOS-2, but was previously diagnosed by a psychologist to have mild to moderate ASD on the CARS.

Table 5.2

Informant Ratings of ASD Symptom Severity on the SRS-2 for the ASD group

	M	*SD*
Total Score	70.36	11.29
DSM-V Scales		
Social Communication and Interaction	69.43	11.22
Restricted Interests/Repetitive Behaviour	72.07	12.90
Symptom Scales		
Social Awareness	69.07	11.55
Social Cognition	66.21	11.83
Social Communication	69.00	10.58
Social Motivation	65.93	12.33
Restricted Interests/Repetitive Behaviour	72.07	12.89

Note. Scores are T-scores. Total score indicates ASD severity according to the following range: normal (≤ 59), mild (60 - 65), moderate (66 - 75), severe (≥ 76). Scores are based on informant ratings for n = 14 ASD participants, as data were missing for two participants. M = mean; SD = standard deviation.

5.2.2. Experimental design

5.2.2.1. Stimuli

Auditory stimuli for the pre-scan and fMRI tasks consisted of vocal affect bursts (e.g., laughter, cries, screams) and neutral voices from the Montreal Affective Voices (MAV; Belin, Fillion-Bilodeau, et al., 2008), as described in detail in previous work by Yap, McLachlan, Scheffer, and Wilson (2018; see Study 3 in Chapter 7). In brief, MAV stimuli were recorded by professional male and female actors for cross-cultural research on auditory emotion processing (Belin, Fillion-Bilodeau, et al., 2008). Here, 42 stimuli corresponding to the six basic emotions, and the neutral category (i.e., monotonous vocalisation of the vowel /a/), with three male and three female voices per category. Previous research has shown that typically developing adults demonstrate over 80% classification accuracy for these stimuli on behavioural testing (Yap et al., 2018; see Chapter 7).

5.2.2.2. Pre-scan task

Prior to the MRI, participants performed a vocal emotion recognition task (Figure 5.1) in a quiet testing room using a laptop computer with external speakers. The task was web-based to allow randomised delivery of MAV stimuli across 42 trials, as previously described (Yap et al., 2018). On each trial, participants listened to an emotional or neutral voice. They were required to select which one of the six basic emotions was expressed in the voice, or alternatively, whether "No Emotion" was expressed (i.e., forced-choice discrimination from seven alternatives). For stimuli assigned to a specific emotion, participants were then asked to rate the intensity of the emotion on a 7-point Likert-type scale (1 = *weak emotion* to 7 = *strong emotion*), providing a measure of emotional arousal. Stimuli classified as "No Emotion" were automatically assigned an intensity rating of "0". Six MAV stimuli were presented per category (42 trials in total), yielding a maximum total accuracy score of 42 points.

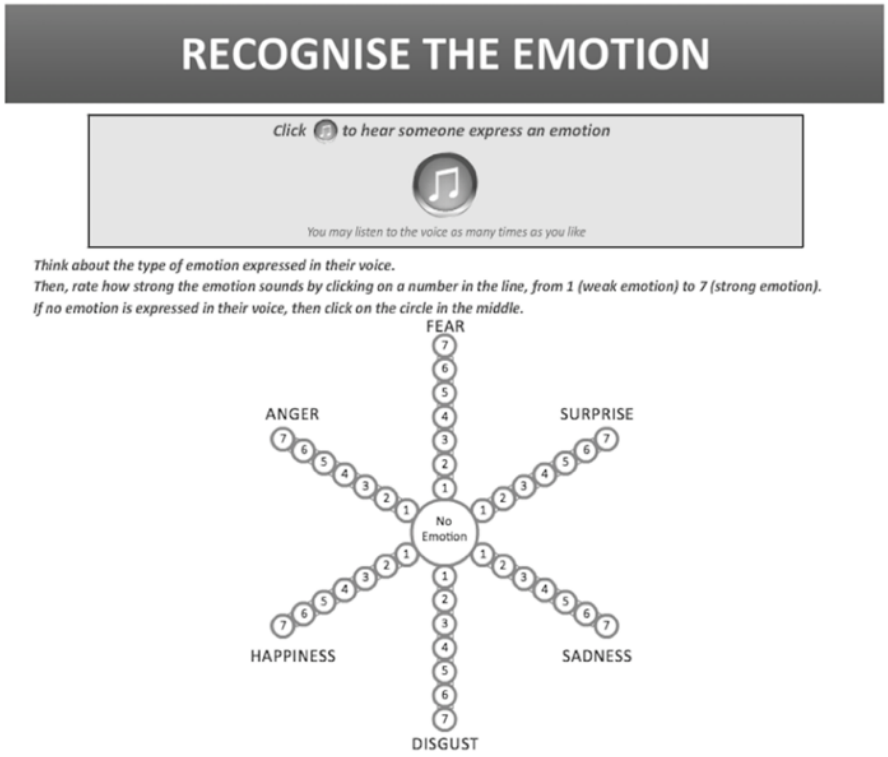


Figure 5.1. Graphic interface of a trial from the computerised pre-scan task. The location of each basic emotion category was randomized around the neutral category after every seven trials. Image source: Yap et al. (2018)

5.2.2.3. fMRI task

The fMRI task (Figure 5.2) was a simplified version of the pre-scan task. It was constructed within Presentation software (Version 16.3; Neurobehavioral Systems, 2013). It consisted of a block design, with six "emotion" blocks that alternated with six "baseline" (gender) blocks. In an emotion block, participants listened to MAV emotional voices and were asked to select between two emotions, specified by words aligned vertically on a screen. In a baseline block, participants listened to MAV neutral voices and were asked to select the gender of the speaker. Across blocks, participants made their selection using a button response unit and were instructed to respond as quickly and accurately as possible. Unlike the pre-scan task, reaction time data was collected and emotional intensity ratings were not measured. Of note, the baseline blocks were designed to control for activation related to the auditory, visual/lexical, and motor processes of no interest inherent to the emotion blocks, so that a contrast between blocks would yield activation specific to the cognitive and affective processes required for emotional voice processing. Each emotion and baseline block was 30 s long and consisted of six trials with an equal number of male and female MAV stimuli. Each emotion block included vocal affect bursts for all six basic emotions.

Prior to scanning, all participants also underwent training on one emotion and one baseline block (six trials each) to ensure that they understood task requirements. Emotional and neutral voices used for training consisted of other MAV stimuli from Belin et al.'s (2008) original battery that were not utilised in the fMRI or pre-scan task. Training was performed on a desktop computer. Participants were also placed in a mock scanner to familiarize them with the MRI environment before their scan.

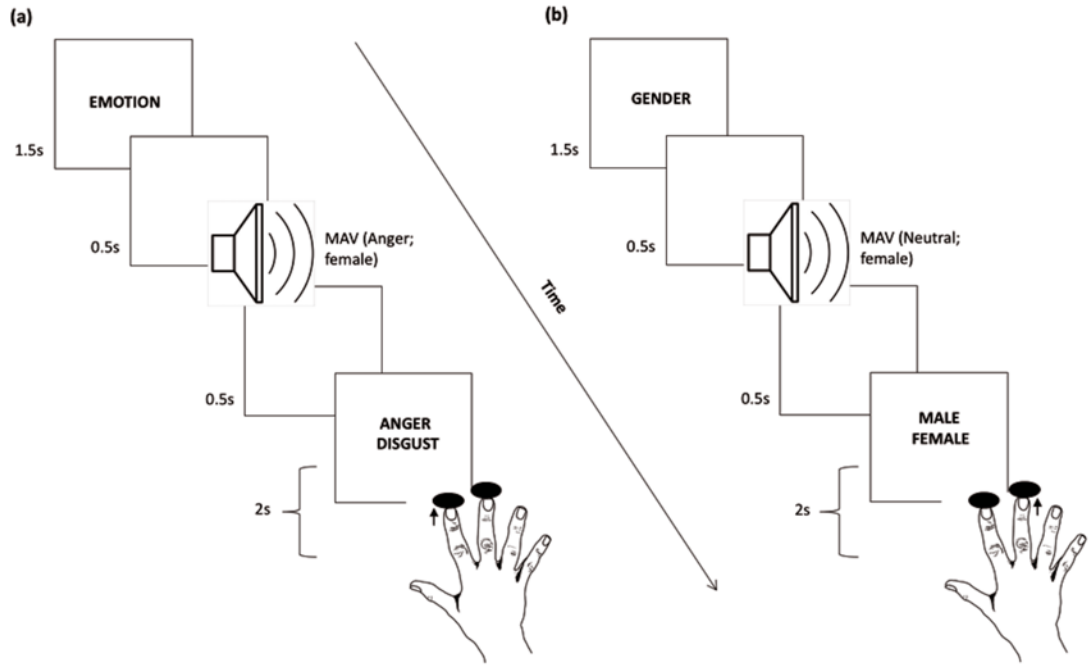


Figure 5.2. Order of events from a trial of an (a) emotion and (b) baseline (gender) block from the fMRI task. Each block began with presentation of the word *EMOTION* or *GENDER*. In each trial of an emotion block, an emotional voice from the MAV was presented through active MR noise-cancelling headphones (OptoACTIVE by Optoacoustics) while participants stared at a blank screen. Next, words corresponding to two basic emotion categories appeared in vertical alignment for 2 s, during which participants used a button response unit (LS-Pair, Lumina by Cedrus) in their dominant hand to select the correct emotion in the voice as quickly and accurately as possible (top word = index finger button; bottom word = middle finger button). Subsequent trials commenced with a new MAV stimulus, presented 1-s after the previous trial. The order of events was similar in each trial of a baseline block, except that participants listened to a neutral voice from the MAV and were required to select the gender of the speaker instead. The baseline blocks were designed to control for auditory, visual/lexical, and motor activation in the emotion blocks. Each emotion and baseline block contained an equal number of male and female stimuli, presented across six trials. Within each block, MAV stimuli and response categories (i.e., top/bottom position of words) were presented in pseudo-randomised order across trials.

5.2.3. Image acquisition

Images were collected on a Siemens 3T Skyra scanner equipped with a 20-channel head coil at the Florey Institute of Neuroscience and Mental Health (Melbourne). The fMRI data were acquired with a whole-brain 2D T2*-weighted gradient-recalled echo-planar imaging (EPI) sequence that had the following parameters: field of view (FOV) = 216 x 216, flip angle = 90°, 44 interleaved slices per volume, slice thickness = 3 mm (no gaps), voxel size 3 x 3 x 3 mm^3, matrix size 72 x 72, echo time (TE) = 30 ms, and repetition time (TR) = 3 s. A total of 120

EPI volumes was acquired per participant within a single run of the in-scanner recognition task (approximately 6 min for a total of 12 blocks). Whole-brain 3D T1-weighted high-resolution structural images (0.9 mm^3 isotropic voxels; matrix size 256 x 256 x 256) were also acquired for coregistration and normalization of the EPI volumes. Participants were instructed to lie still during data acquisition, and pads were positioned around their heads to minimize movement.

5.2.4. Data analysis (fMRI)

5.2.4.1. Pre-processing

The fMRI data were pre-processed using Statistical Parametric Mapping software (SPM12, Version 665; Wellcome Trust Centre for Neuroimaging, 2014). The first pre-processing steps included slice-timing correction to the first slice acquired, spatial realignment to the image that had a within-brain centre-of-mass closest to the median centre-of-mass (target image selected using iBrain, Version 5.7; Abbott et al., 2011), and coregistration of the T1 image to the mean EPI. Next, the T1 image was reoriented to shift its zero coordinate to the anterior commissure origin in Montreal Neurological Institute (MNI) space, and each EPI image was then coregistered to the newly realigned T1 image. The T1 image was segmented to compute a forward deformation field, used to normalize the EPI images to MNI space (3 mm^3 isotropic voxels). Finally, EPI images were spatially smoothed using a Gaussian kernel of 8 mm (full-width, half-maximum). All transformation was performed using affine registration and all interpolation was performed using a 7^{th}-degree B-spline.

5.2.4.2. Whole-brain analyses

Statistical parametric maps for each voxel were computed in SPM12 using the general linear model (GLM). Both random-effects (RFX) and fixed-effects (FFX) models were used to determine whole-brain activation within each group and differences in whole-brain activation

between groups at the population and sample levels, respectively. The RFX model accounts for both within-subject and between-subject variance, and can therefore be used to make inferences about activation in the wider ASD and general populations (see Friston, Holmes, Price, Büchel, & Worsley, 1999; Penny & Holmes, 2003). In contrast, the FFX model accounts for within-subject variance alone, and can therefore only be used to make inferences about activation in the specific ASD and control samples assessed here (K. J. Friston et al., 1999; Penny & Holmes, 2003).

RFX analyses were performed using a multi-level approach (Holmes & Friston, 1998). At the first-level, time-series data across EPI volumes for each participant were independently entered into a single-subject design matrix to determine parameter estimates (i.e., beta values) for that participant. Accordingly, 120 data points (corresponding to the total number of EPI volumes) were used to determine parameter estimates per participant based on scan-to-scan variability or within-subject variance. The design matrix for each participant contained: (a) a single regressor of interest, which modelled the canonical haemodynamic response function (HRF) to the emotion block, (b) six motion correction parameters as covariates of no interest, and (c) a constant term (Figure 5.3). Of note, the design matrix did not contain an additional regressor of interest to model the canonical HRF corresponding to the baseline block. This was omitted to avoid "over-parameterisation", since the constant term—which represents the estimated overall signal minus the effects of the emotion regressor, motion covariates, and error—essentially models the baseline here (Pernet, 2014). A contrast image was created to reflect the difference in parameter estimates between the emotion and baseline conditions (i.e., "emotion > baseline"), where the contrast vector was specified as $c = [1\ 0\ 0\ 0\ 0\ 0\ 0\ 0]$ or simply $c = [1]$.

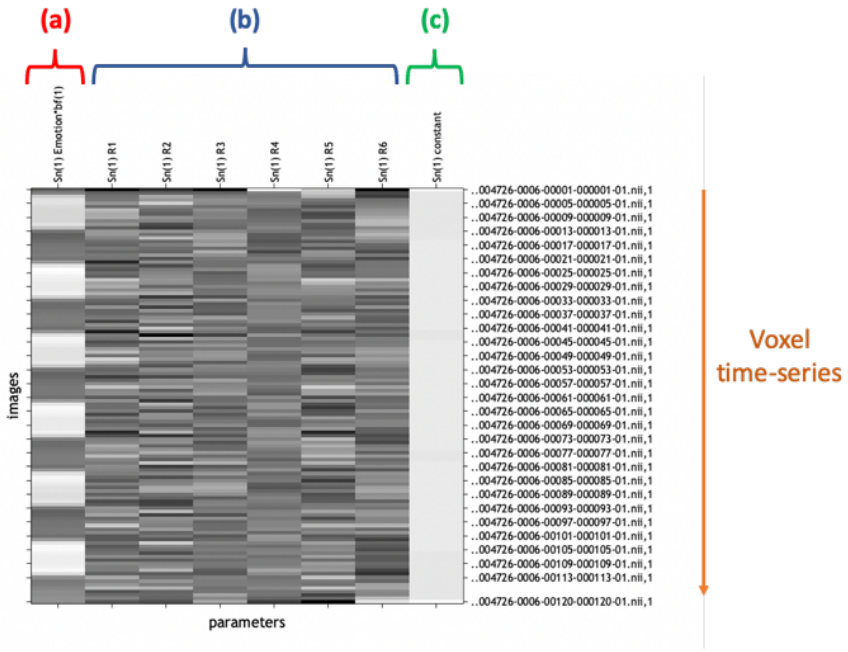


Figure 5.3. Single-subject design matrix from SPM12, which models the expected BOLD signal in each voxel across 120 time points (120 EPI volumes; TR = 3s) according to the following predictors: (a) one regressor of interest corresponding to the canonical HRF of emotion blocks, (b) six motion covariates of no interest, and (c) the constant term.

At the second-level, each participant's contrast image was jointly entered into a multi-subject design matrix to determine group effects based on the random variability between subjects. For within-group analyses, 16 data points (i.e., 16 contrast images per group) were analysed using one-sample t-tests, which determined the average activation resulting from the "emotion > baseline" contrast per group. For between-groups analyses, 32 data points (i.e., 16 contrast images x 2 groups) were analysed using two-sample t-tests, which compared the average activation resulting from the "emotion > baseline" contrast between groups. Specifically, the two-sample t-tests determined whether the ASD group showed increased or decreased activation relative to controls (i.e., "ASD > controls" and "ASD < controls" contrasts).

Unlike RFX, FFX analyses were not subject to a multi-level approach. They were performed entirely at the first-level by concatenating all participants' time-series data (i.e., total number of scans across participants) into a large multi-subject design matrix. Therefore, a relatively

large number of data points (i.e., 120 volumes x 16 participants per group) were analysed to determine the average activation within each group ("emotion > baseline" contrast for one-sample t-test) and to compare the average activation between groups ("ASD > controls" and "ASD < controls" contrasts for two-samples t-tests). Importantly, group effects from FFX analyses were based on scan-to-scan variability alone.

For each contrast from both RFX and FFX group analyses, cluster-based thresholding was used to determine significant activation at a family-wise error (FWE) corrected cluster-wise threshold of $p < .05$ (voxel-wise primary threshold of $p < .001$), unless specified otherwise. An explicit whole-brain mask (i.e., *mask_ICV.nii* from the SPM12 package, no threshold) was specified for all RFX and FFX group analyses. A high-pass filter was specified with a cut-off of 120 s to remove low-frequency signal variation.

5.3. Results

5.3.1. Classification of vocal affect bursts and neutral voices on the pre-scan task

On the pre-scan task, the ASD group was significantly worse at identifying neutral voices compared to controls (Figure 5.4), $t(30) = 2.31$, $p = .033$, $d = 0.82$. Post-hoc inspection of errors revealed that neutral voices were most often confused with surprise (on 11% of neutral trials) in the ASD group. One ASD participant never identified neutral voices correctly, consistently selecting surprise despite scoring reasonably well across the emotion trials (75% mean total accuracy). After removing this participant from the analysis, lower performance was still observed for the ASD group compared to controls (ASD: $M = 85.56\%$, $SD = 15.26$; Controls: $M = 95.83\%$, $SD = 7.45$) suggesting a robust group difference with large effect size, $t(20.03) = 2.36$, $p = .029$, $d = 0.86$, with surprise still being the most common error (on 5% of

neutral trials). The ASD participants assigned low emotional intensity ratings (e.g., ratings of 1-3 out of a maximum of 7) to neutral voices which were confused as being emotional.

Post-hoc analyses showed that the control group had significantly higher classification accuracy for the neutral category than for total emotion classification accuracy (collapsed across all six basic emotions), $t(15) = 6.13$, $p < .001$, $d = 2.10$. In contrast, there was no significant difference in the ASD group $t(15) = 0.03$, $p = .98$. This suggests that controls, but not the ASD group, found neutral voices easier to identify than emotional voices in general, whereas ASD participants were more likely to attribute emotional expressions to the neutral voices. Of note, however, both groups rarely misattributed the neutral expression to emotional voices (e.g., misclassifying basic emotions as being neutral), with the ASD and control participants only committing these errors on 0.01% and 0.02% of all emotional trials (e.g., total emotional trials = 16 participants x 36 trials), respectively.

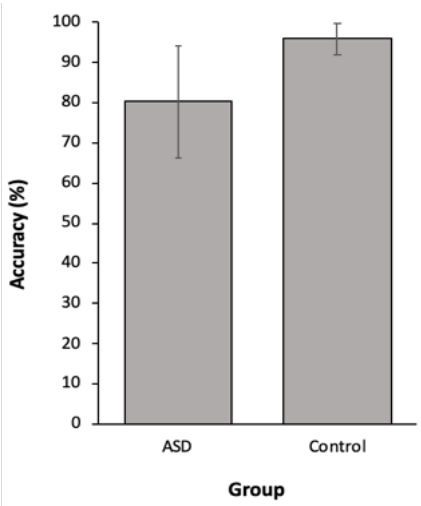


Figure 5.4. Group mean performance on the pre-scan task for the classification of neutral voices. Error bars represent 95% confidence intervals.

For vocal affect bursts correctly identified as emotions, the ASD and control groups showed a similar classification rate of approximately 80% total accuracy for the six basic emotions

(ASD: $M = 80.38\%$, $SD = 8.02$; Controls: $M = 78.65\%$, $SD = 8.83$). A two-way mixed ANOVA revealed no interaction between group and basic emotion category on classification accuracy (Figure 5.5a), $F(2.99, 89.72) = 1.11$, $p = .35$, $\eta^2 = 0.04$, and no main effect for group, $F(1, 30) = 0.34$, $p = .57$, $\eta^2 = 0.01$. There was a main effect for emotion category, $F(2.99, 89.72) = 20.73$, $p < .001$, $\eta^2 = 0.41$. Bonferroni-corrected post-hoc comparisons revealed that accuracy for happiness was significantly higher than all other emotions ($p < .01$) across both groups, while accuracy for sadness was higher than fear, anger, and surprise ($p < .01$). In addition, accuracy for disgust was higher than anger ($p < .001$). The ASD and control groups showed similar patterns of accuracy, with the exception that the ASD group identified fear less accurately than surprise, with the reverse seen in controls (Figure 5.5a). This is consistent with research on the general population, which shows high rates of confusion between voices expressing fear and surprise (Belin, Fillion-Bilodeau, et al., 2008; Pell et al., 2009; Simon-Thomas, Keltner, Sauter, Sinicropi-Yao, & Abramson, 2009; Yap et al., 2018).

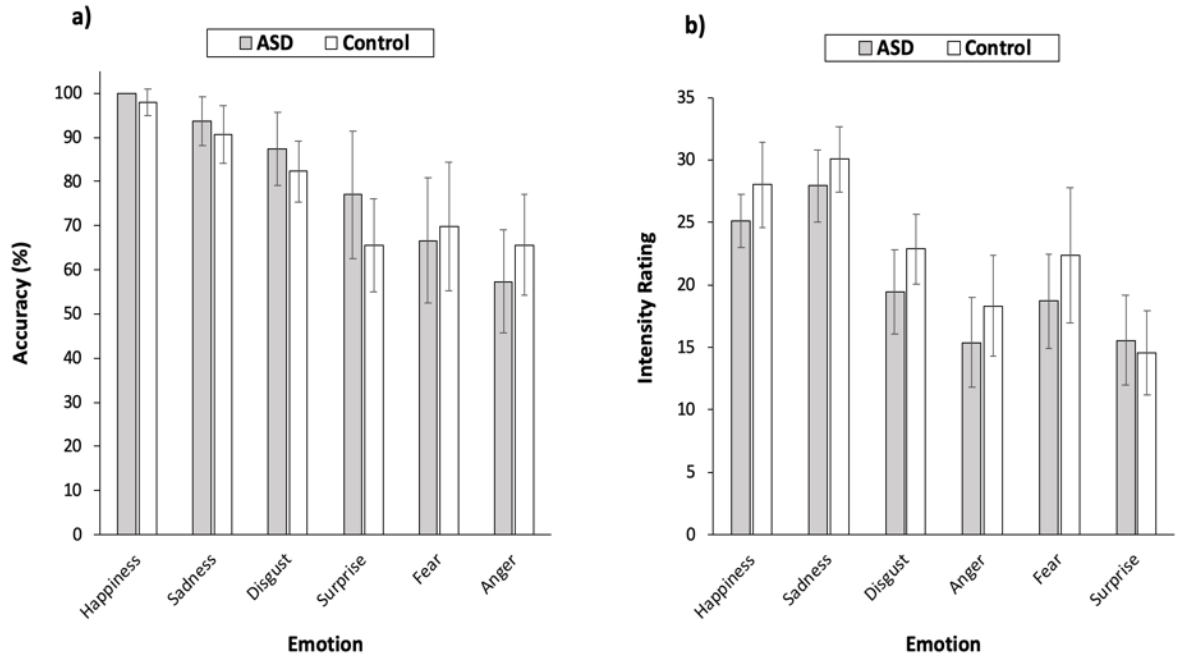


Figure 5.5. Group mean performance on the pre-scan task for (a) accuracy of emotion classification and (b) emotion intensity ratings of each basic emotion category. Error bars represent 95% confidence intervals.

Analyses were also performed for group mean emotion intensity ratings of vocal affect bursts that were accurately classified (Figure 5.5b). There was no interaction between group and basic emotion category on emotion intensity ratings, $F(3.46, 103.93) = 0.68$, $p = .64$, $\eta^2 = 0.02$, and no main effect for group, $F(1, 30) = 3.12$, $p = .09$, $\eta^2 = 0.09$. Differences emerged again for the emotion categories across both groups, $F(3.49, 103.93) = 26.68$, $p = .00$, $\eta^2 = 0.47$. Bonferroni-corrected post-hoc comparisons revealed that intensity ratings for sadness and happiness were significantly higher than for all other emotions ($p < .05$), and intensity ratings for disgust were higher than surprise ($p < .001$). The two groups showed a similar pattern of intensity ratings across the emotion categories (Figure 5.5b). Within each group, intensity ratings for each basic emotion correlated positively with classification accuracy for that emotion [ASD: $r(14) = .74$ to $.95$, $p < .001$; Controls: $r(14) = .50$ to $.93$, $p < .05$], with the exception of happiness in ASD, given its ceiling effects for accuracy.

5.3.2. fMRI of vocal affect burst recognition

5.3.2.1. fMRI task performance

Both the ASD and control groups showed highly accurate task performance on the emotion and baseline blocks of the fMRI task (Figure 5.6a). High performance in each group supports the utility of the fMRI task, indicating that it was appropriate for eliciting activation in brain regions involved with processing vocal affect bursts. A two-way mixed ANOVA revealed no significant interaction effect between group and block on classification accuracy (i.e., no significant difference in emotion versus baseline task performance in either group), $F(1, 30) = 0.90$, $p = .35$, $\eta^2 = 0.03$, and no main effect for group, $F(1, 30) = 0.36$, $p = .55$, $\eta^2 = 0.01$. There was a main effect for block, $F(1, 30) = 6.01$, $p = .02$, $\eta^2 = 0.17$, with higher accuracy for the identification of gender (baseline block) compared to emotions when performance was collapsed across both groups. For the reaction time data, a separate mixed ANOVA of correct

trials (Figure 5.6b) revealed no significant interaction effect between group and block, $F(1, 30) = 0.26$, $p = .62$, $\eta^2 = 0.01$, and no main effect for group, $F(1, 30) = 0.39$, $p = .54$, $\eta^2 = 0.01$. Again, there was a main effect for block, with faster reaction times for gender versus emotion identification when performance was collapsed across both groups, $F(1, 30) = 28.69$, $p < .001$, $\eta^2 = 0.49$.

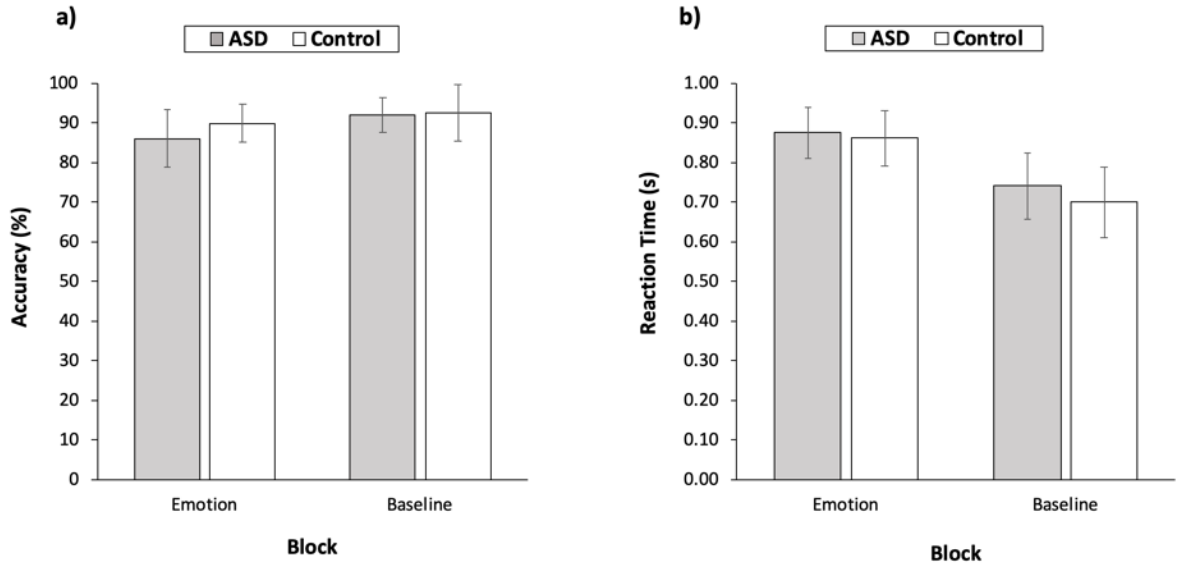


Figure 5.6. Group mean performance on the fMRI task for (a) classification accuracy on the emotion and baseline blocks, and (b) reaction time (on correct trials) for each block. Error bars represent 95% confidence intervals.

5.3.2.2. fMRI analysis

5.3.2.2.1. Whole-brain analyses (RFX): activation within ASD and control groups

Whole-brain RFX analyses revealed four significant clusters of activation in the ASD group ($k \geq 159$) and eight in the control group ($k \geq 78$). Functional maps of the significant clusters within each group are shown in Figure 5.7, and MNI coordinates of local maxima (peak voxels) per cluster are listed in Table 5.3. Regions of significant activation that were common to both groups include the bilateral precentral gyri, bilateral IFG (pars triangularis and opercularis), right STS (extending to the banks of the middle and superior temporal gyri; hereafter referred to as the STS/MTG/STG), and left fusiform gyrus. Cerebellar activation was left-lateralised

in the ASD group and right-lateralised in controls. The ASD group alone showed significant activation in the left STS/MTG, bilateral thalamus, right hippocampus, and right parahippocampal gyrus. The control group alone showed significant activation in the right STG, bilateral anterior insula, bilateral orbitofrontal cortex (OFC; IFG pars orbitalis), left superior and inferior parietal gyri, and several bilateral occipital structures (e.g., primary visual area/calcarine sulcus, lingual gyrus, superior/middle/inferior occipital gyri). However, these differences were not significant on direct comparison between the groups based on RFX analyses (see Section 5.3.2.2.2).

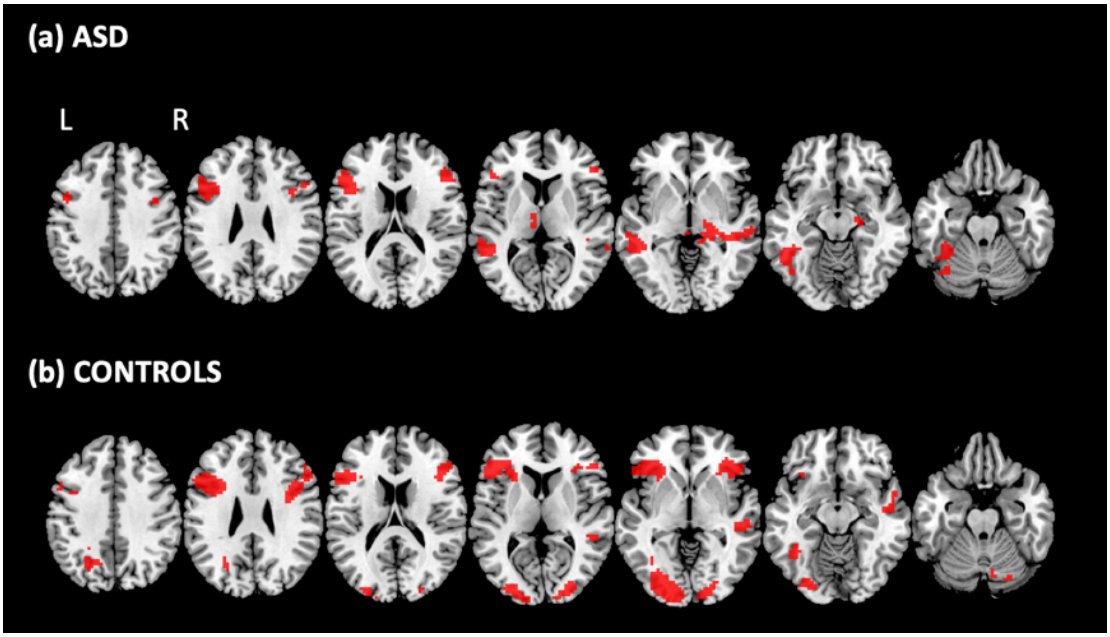


Figure 5.7. Clusters of significant activation from the RFX analyses of the "emotion > baseline" T-contrast in the (a) ASD group and (b) control group at a cluster-wise FWE-corrected threshold of $p < .05$ (voxel-wise primary threshold of $p < .001$). Activation images are shown overlaid on axial T1-weighted images in MNI template space. L = left; R = right.

Table 5.3

Whole-Brain RFX Analyses: Peak Voxels from Significant Clusters within the ASD and Control Groups

	Local maxima				
Cluster Size (*k*)	Region	*x*	*y*	*z*	T-score
ASD					
365	L middle temporal gyrus	-51	-43	2	7.64
	L cerebellum (VI)	-36	-37	-28	7.44
	L fusiform gyrus	-36	-46	-22	6.85
	L inferior temporal gyrus	-45	-49	-16	6.5
247	R hippocampus	27	-28	-4	7.06
	R superior temporal gyrus	57	-25	-4	5.61
	R thalamus	21	-31	-1	5.25
	R brainstem*	21	-16	-10	5.2
	R middle temporal gyrus	45	-34	2	4.99
	R thalamus	18	-28	2	4.78
	L thalamus	-6	-10	8	4.66
	R lingual gyrus	12	-37	-4	4.42
289	L inferior frontal gyrus (triangularis)	-48	26	17	6.73
	L precentral gyrus	-45	8	35	5.25
159	R inferior frontal gyrus (triangularis)	51	35	11	5.23
	R precentral gyrus	39	2	35	5.19
	R inferior frontal gyrus (opercularis)*	36	11	26	4.58
Controls					
682	L inferior frontal gyrus (triangularis)	-42	17	26	8.23
	L precentral gyrus	-39	8	29	7.50
	L insula	-27	20	8	4.92
	L inferior frontal gyrus (orbitalis)	-33	23	-10	4.83
542	L fusiform gyrus	-39	-55	-7	7.58
	L middle occipital gyrus	-30	-76	-4	7.41
	L lingual gyrus	-21	-82	-4	5.84
	L calcarine sulcus	-12	-97	-4	5.42
	L inferior occipital gyrus	-24	-94	-10	4.36
345	R insula	36	32	5	5.92
	R precentral gyrus	48	8	32	5.73
	R inferior frontal gyrus (triangularis)	48	20	23	5.67
	R inferior frontal gyrus (opercularis)	57	20	32	5.32
	R inferior frontal gyrus (orbitalis)	36	35	-4	5.18
	R putamen	27	20	2	5.04
163	R cerebellum (Cr II)	12	-76	-34	6.18
	R cerebellum (Cr I)	12	-79	-28	5.94
	R cerebellum (VIII)	27	-67	-49	5.63
	R cerebellum (VI)	27	-76	-22	4.28
153	R calcarine sulcus	15	-94	-1	6.09
	R middle occipital gyrus	27	-91	11	5.5
	R cuneus	12	-97	11	4.15
	R inferior occipital gyrus	27	-91	-10	3.83
134	R superior temporal gyrus	51	-25	-4	7.92

	Local maxima				
Cluster Size (*k*)	Region	*x*	*y*	*z*	T-score
114	L inferior parietal gyrus	-30	-58	47	5.29
	L middle occipital gyrus	-27	-67	38	4.76
	L precuneus	-15	-61	38	4.74
78	L putamen	-21	-4	14	4.92

Note. Results are from the "emotion > baseline" T-contrast, thresholded at a cluster-wise FWE-corrected level of $p < .05$ (voxel-wise primary threshold of $p < .001$). The table shows cluster size (*k*), along with MNI coordinates and T-scores from the three highest peak voxels from each structure within the cluster. Peak voxels are separated by more than 8 mm. Peak voxels are labelled according to the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Asterisks (*) indicate the approximate region for peak voxels that do not have a corresponding label from the AAL atlas. L = left; R = right.

5.3.2.2.2. Whole-brain analyses (RFX): direct comparison between groups

Whole-brain RFX analyses revealed no significant clusters of activation when the two groups were directly compared (i.e., "ASD > controls" and "ASD < controls" contrasts). These findings suggest that significant group differences in brain activation underlying the recognition of vocal affect bursts cannot be inferred at the population level. A trend for differences only emerged at a voxel-wise uncorrected threshold level of $p < .001$ for the "ASD > controls" contrast. Specifically, the ASD group showed a trend for greater activity in the right precentral and postcentral gyri, right IFG (pars opercularis), left medial prefrontal cortex (mPFC), right insula, left MTG, right hippocampus, and left cerebellum. MNI coordinates of peak voxels are listed in Appendix D.

Of note, the absence of significant group differences could reflect the effects of low statistical power, since only a small number of data points ($n = 32$ contrast images across 16 participants x 2 groups) were subjected to the RFX analyses. To further explore the data, whole-brain FFX analyses were additionally conducted to determine activation within each group, as well as group differences in activation, for these specific cohorts. As aforementioned, FFX analyses have more statistical power than RFX analyses, since they make use of a large number of data

points (n = 120 EPI volumes x 16 participants per group). However, findings from FFX analyses cannot be generalised to the wider population from which the cohorts were sampled, since they do not account for between-subject variance.

5.3.2.2.3. Whole-brain analyses (FFX): activation within groups and direct comparison between groups

Whole-brain FFX analyses revealed 10 significant clusters of activation in the ASD group ($k \geq 26$) and seven in the control group ($k \geq 69$) at a stringent FWE-corrected cluster threshold of $p < .05$ (voxel-wise primary threshold of $p < .0001$). Functional maps of the significant clusters within each group are shown in Figure 5.8, and MNI coordinates of local maxima per cluster are listed in Table E.1 (Appendix E). Several regions with significant activation were common to both groups, including the bilateral IFG (pars triangularis and opercularis), STS/MTG, insula, OFC, and superior temporal poles. Both groups also had significant activation in the left superior and inferior parietal cortices, the supplementary motor area (SMA), and the bilateral precentral gyri, fusiform gyri, occipital lobes (e.g., calcarine sulcus, lingual gyrus, and the superior, middle & inferior occipital gyri), and cerebelli. Of note, some of these regions were also common to both groups when within-group RFX analyses were performed (see Section 5.3.2.2.1).

For the direct comparison of activation between groups, whole-brain FFX analyses revealed no significant clusters of activation for the contrast of "ASD < controls" at an FWE-corrected cluster threshold of $p < .05$ (voxel-wise primary threshold of $p < .001$). However, FFX analyses revealed six significant clusters ($k \geq 85$) for the opposite contrast of "ASD > controls", as shown in Figure 5.8c (see Table E.2 in Appendix E for MNI coordinates of local maxima per cluster). Regions with significantly higher activation in the ASD group relative to controls

included the left IFG (pars triangularis) and the bilateral STG and MTG (inclusive of the STS only in the left hemisphere). Other regions of enhanced activation in the ASD group included the following: (a) right amygdala, precentral gyrus, and postcentral gyrus, (b) left middle frontal gyrus (dorsolateral prefrontal cortex), middle temporal pole, parahippocampal gyrus, and angular gyrus, and (c) bilateral hippocampi, precuneus, occipital lobes (e.g., calcarine sulcus, lingual gyri, cuneus, superior/middle/inferior occipital gyri), and cerebelli. Overall, the FFX analysis of the "ASD > Controls" contrast suggests that significant group differences can be inferred at the sample level, despite the RFX analysis showing no evidence of significant group differences which can be inferred at the population level.

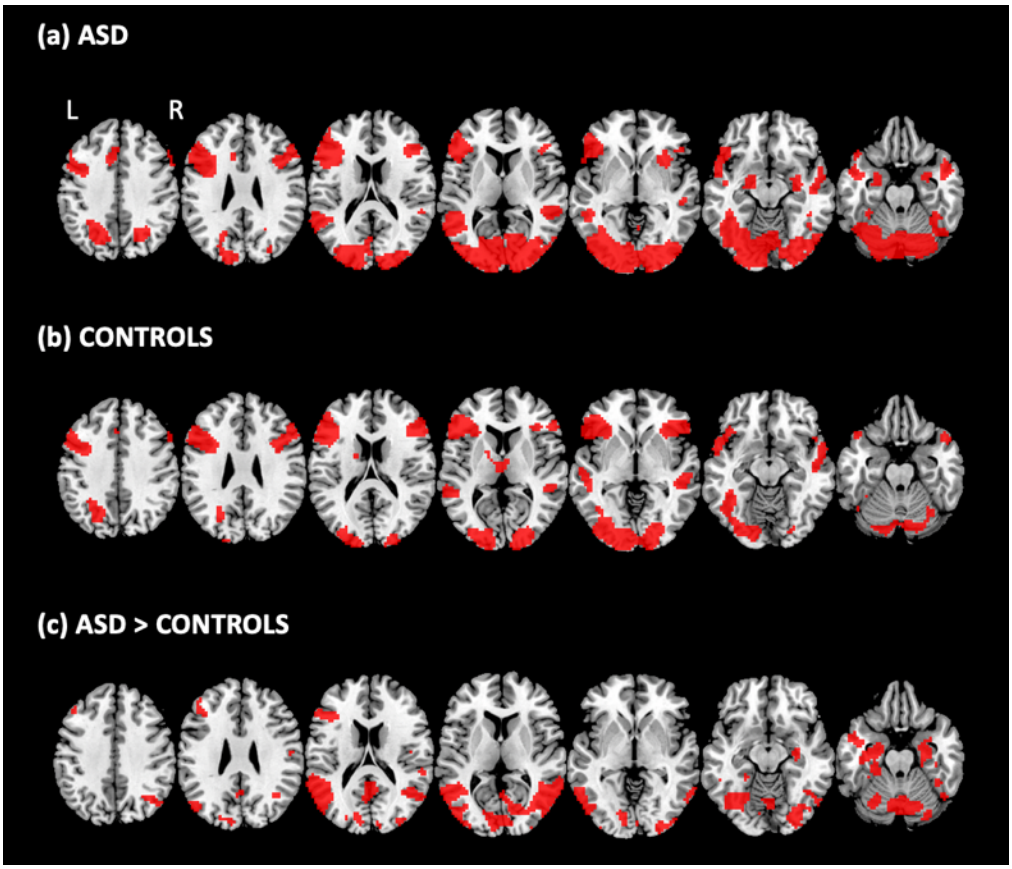


Figure 5.8. Clusters of significant activation from the FFX analyses of the "emotion > baseline" T-contrast in the (a) ASD group and (b) control group at a cluster-wise FWE-corrected threshold of $p < .05$ (voxel-wise primary threshold of $p < .0001$). This figure also shows (c) clusters of significantly higher whole-brain activation in the ASD group relative to controls at a cluster-wise FWE-corrected threshold of $p < .05$ (voxel-wise primary threshold of $p < .001$). Activation images are shown overlaid on axial T1-weighted images in MNI template space. L = left; R = right.

5.3.2.3. Correlations between activity in emotional voice areas and symptom severity in the ASD group

Secondary analyses were conducted on data from the ASD group to determine whether activity in emotional voice areas correlated with informant ratings of symptom severity on the SRS-2. Specifically, these regions-of-interest (ROIs) corresponded to parts of the bilateral IFG (pars triangularis and opercularis), left STS/MTG, and right STS/MTG/STG that showed significant activation within the ASD group under the RFX model (see Section 5.3.2.2.1). Appendix F includes a detailed description of the procedure undertaken to create inclusive masks of each ROI. Activity in each ROI was indexed by the mean of parameter estimates (i.e., beta values) across voxels. For each participant, mean parameter estimates in each ROI were extracted from their "emotion > baseline" contrast image using the REX toolbox for SPM (Gabrieli Lab, 2013).

Two participants were excluded from the correlational analyses due to missing SRS-2 data (i.e., only 14 participants included). Scores for each SRS-2 scale are shown in Table 5.2, with the total score indicating symptom severity in the moderate range. Higher SRS-2 scores indicated more severe deficits. Non-parametric tests (Spearman's rank-order correlation coefficient) were used in place of parametric tests (Pearson's correlation coefficient) to determine whether a monotonic relationship existed between activity in each ROI and SRS-2 scores for each symptom subscale and the total score. Spearman's coefficients are relatively robust against outliers (Schober, Boer, & Schwarte, 2018), and hence more appropriate for the data here, since one participant was an extreme outlier on mean parameter estimates of each ROI (i.e., greater than the upper quartile plus three times the interquartile range).

Among the ROIs tested, only activity in the IFG correlated significantly with SRS-2 scores. For the right IFG, activity in the pars triangularis alone correlated positively with SRS-2 scores on the following scales: (i) total score [$r_s(12) = .58$, $p = .031$], (ii) social awareness [$r_s(12) = .54$ $p = .045$], and (iii) restricted interests/repetitive behaviour (RRB), [$r_s(12) = .66$ $p = .010$]. For the left IFG, activity in the pars triangularis correlated positively with scores for social cognition [$r_s(12) = .58$, $p = .030$], and activity in the pars opercularis correlated positively with scores for social awareness [$r_s(12) = .64$, $p = .014$]. Scatterplots of these correlations are shown in Appendix G.

5.4. Discussion

Study 1 assessed behavioural performance and brain activation associated with the recognition of vocal affect bursts in individuals with ASD compared to controls. The ASD group demonstrated impaired vocal emotion recognition on the pre-scan task, reflected by their inaccurate classification of neutral voices as expressing basic emotions. However, when presented with emotional voices, they classified basic emotions as well as controls and engaged similar brain regions to do so. No significant differences in brain activation were found between groups based on RFX analysis, although FFX analysis revealed that the ASD group demonstrated significantly higher activation relative to controls in several brain regions. It should be noted however that this latter inference is only relevant to the specific cohort of participants ($n = 16$) studied, and not the wider population of individuals with ASD.

5.4.1. Impaired vocal emotion recognition in ASD

Evidence for impaired vocal emotion recognition in the ASD group emerged on trials of neutral voices in the pre-scan task. Specifically, the ASD group was less able to identify whether an emotion was present or not for neutral voices, whereas controls performed at ceiling levels. In

contrast, no significant group differences were found on trials of emotional voices in the pre-scan task, with similar patterns of accuracy and intensity ratings observed between groups. Similarly, the ASD group demonstrated intact performance on emotion blocks of the fMRI task, on which they were exclusively presented with emotional voices to classify.

It is interesting that reduced performance by the ASD group relative to controls was limited to the classification of neutral voices alone. Unlike emotional stimuli, neutral stimuli from the MAV had a flat pitch contour (i.e., monotonous voice), which was expected to distinguish them as having "no emotion" rather than one of the six basic emotions. The ASD group most commonly confused neutral voices as conveying surprise, although stimuli for surprise had higher mean f0 variability and were briefer than the neutral stimuli. Further investigation is warranted to explore the confusion between neutrality and surprise in non-linguistic vocalisations. Importantly, the inability to recognise that a voice lacks emotional expressivity may contribute to social communication deficits in ASD, since individuals may misattribute an affective state to others and respond inappropriately.

Previous studies have also shown that individuals with ASD have difficulty distinguishing neutral from emotional voices (Hubbard, Faso, Assmann, & Sasson, 2017; Vannetzel et al., 2011). For example, Vannetzel and colleagues (2011) found that children with PDD-NOS were worse than controls at judging emotional congruence between pairs of neutral-neutral and neutral-emotional non-linguistic vocalisations. Hubbard and colleagues (2017) found that adults with ASD were worse than controls at discriminating neutral from emotional prosody (e.g., angry, happy, sad, interested) in speech samples recorded by other typically-developing individuals and individuals with ASD. Relative to controls, the ASD group also rated the neutral prosody as sounding less natural. These findings, like those from the present study,

suggest that individuals with ASD tend to over-attribute emotional states to neutral voices, likely contributing to their social communication deficits. Of note, poor recognition of neutral expressions has also been observed in the face modality, with studies reporting that individuals with ASD attribute negative valence to neutral faces at higher rates than controls (Eack et al., 2015; Vannetzel et al., 2011).

5.4.2. Neural correlates of vocal emotion recognition in ASD and controls

In-scanner, the ASD and control groups were able to classify emotional voices at ceiling levels, yielding brain activation that reflected correct task performance, rather than guessing. RFX and FFX analyses of the fMRI data revealed significant activation in task-relevant regions common to both groups. Only findings from the RFX analyses will be discussed in this section, since they can be generalised to the wider population of individuals with ASD and typically-developing controls.

Under the RFX model, the ASD and control groups demonstrated activation in regions that serve social cognition (e.g., bilateral IFG, right STS with adjacent MTG and STG, left fusiform gyrus). Importantly, the IFG and STS (plus MTG and STG) are sensitive to the processing human voices, particularly emotional ones (Bestelmeyer et al., 2014; Ethofer et al., 2012; Frühholz & Grandjean, 2013; Grandjean et al., 2005; Meyer et al., 2005; Morris et al., 1999; Schirmer & Kotz, 2006). The STS is connected to the ipsilateral IFG, constituting the antero-ventral auditory "what/how" pathway (Alain, Arnott, Hevenor, Graham, & Grady, 2001; Ethofer et al., 2012). Multi-step models for emotional voice processing have proposed that the STS is responsible for extracting acoustic features of the voice and integrating them into an "emotional gestalt", while the IFG enables individuals to make higher-order, cognitive evaluations about emotional content based on semantic representations (Bestelmeyer et al., 2014; Brück, Kreifelts, & Wildgruber, 2011; Frühholz & Grandjean, 2013; Schirmer & Kotz,

2006). Further, the IFG and STS also serve other social cognitive functions like theory of mind (Bzdok et al., 2012; see also Section 3.2.2) and are considered by some researchers to support the self-other "mirroring" of affective states in empathy (Carr et al., 2003; see also Section 3.3.2).

It is interesting that both groups also engaged the fusiform gyrus to perform the task. The fusiform gyrus is typically involved with face processing (Grill-Spector et al., 2004; Kanwisher et al., 1997; see also Section 3.4.3), including the mental imagery of faces (Ishai, Ungerleider, & Haxby, 2000; O'Craven & Kanwisher, 2000). Since vocal affect bursts are often accompanied by facial expressions in real-life settings, it is possible that the auditory stimuli elicited visual representations of that emotion in both groups. This suggests that the ASD participants and controls used cross-modal processing strategies to accurately classify emotions in the voice. Significant activation common to both groups was also found in the precentral gyrus. While the precentral gyrus is primarily known for its role in motor control, studies have reported that it also responds to the perception of emotional voices, potentially reflecting the automatic preparation of orofacial gestures that mirror the emotion perceived in the voice (Alba-Ferrara, Hausmann, Mitchell, & Weis, 2011; Bestelmeyer et al., 2014; Warren et al., 2006). Both groups also showed significant activation in the cerebellum, which may have served non-motor functions like auditory recognition, emotion processing, and executive function (Clausi et al., 2017; McLachlan & Wilson, 2017; O'Halloran, Kinsella, & Storey, 2012).

In addition to these commonalities, RFX analyses showed activations that were "unique" to each group at the FWE-corrected cluster-wise significance threshold specified. For example, the ASD group alone showed significant activation in memory structures (i.e.,

parahippocampal gyrus, hippocampus), suggesting their engagement in episodic memory retrieval, including the recall of learnt strategies to assist their classification of emotional voices. The control group alone showed significant activation in additional frontal and temporal regions for salience processing and social cognition more broadly (e.g., anterior insula, OFC), parietal regions for the orienting of attention (e.g., superior and inferior parietal gyri), and occipital regions.

Importantly, however, RFX analyses comparing activation between groups yielded no significant group differences in any brain region, including those "unique" to each group. Only a trend for group differences was found at an uncorrected significance threshold, with the ASD group showing greater activation than controls in the hippocampus, cerebellum, and regions serving social cognition (e.g., IFG, insula, MTG), motor, and somatosensory processing (e.g., precentral and postcentral gyri). No trend was found for reduced activation in the ASD group. These findings may hint at the potential for the wider ASD population to rely on additional cognitive resources to recognise vocal affect bursts, although this is speculative and would require further exploration using a larger sample. It is interesting to note that these findings are consistent with fMRI studies on the processing of basic emotions in speech prosody in ASD, which also showed a trend for higher brain activation in ASD versus controls at uncorrected significance thresholds only (Eigsti et al., 2012; Gebauer et al., 2014).

Additionally, it should be noted that for the ASD group, activation in the bilateral IFG (under the RFX model) correlated positively with informant-ratings of symptom severity on the SRS-2. This indicates that ASD participants with more severe deficits in various aspects of social communication and restricted interests/repetitive behaviours used more cognitive resources to make emotional judgements about the vocal affect bursts. An fMRI study examining brain

activation in ASD during the observation of emotional faces also reported a relationship between activity in the IFG and social impairment (on different diagnostic measures), although the correlations were found in the opposite direction, where lower brain activation was associated with more severe deficits (Dapretto et al., 2005). Discrepancies between the two sets of findings are likely due to differences in the modality of stimuli used (e.g., voices versus faces) and task requirements (e.g., cognitive evaluation versus passive viewing).

5.4.3. Atypical brain activation specific to the ASD cohort in this study

Overall, the RFX analyses yielded no conclusive evidence for atypical brain activation associated with the recognition of vocal affect bursts in the wider ASD population. This could be due to low statistical power and/or high variability of activation between participants in the ASD and control groups (i.e., between-subject variance). Accordingly, group differences in brain activation were further explored using FFX analyses, which have higher statistical power but account for within-subject variance alone (K. J. Friston et al., 1999; Penny & Holmes, 2003).

Unlike RFX analyses, FFX analyses revealed significant group differences, indicating atypical brain activation specific to this cohort of 16 ASD participants (i.e., not generalisable to other individuals with ASD). The ASD group had higher activation than controls in emotional voice areas (e.g., bilateral IFG, left STS), motor and somatosensory regions (e.g., precentral and postcentral gyri), visual regions (e.g., occipital structures, fusiform gyrus), and regions serving executive function and semantic processing (e.g., middle frontal gyrus, cerebellum, middle temporal pole). They also had higher activation in the amygdala and memory structures of the default mode network (e.g., hippocampus, parahippocampal gyrus, precuneus, angular gyrus). Enhanced activation in the ASD group could potentially reflect decreased efficiency and

increased cognitive demands (e.g., cognitive control, recall of emotional memories, visual imagery) to recognise vocal affect bursts. Of note, these FFX findings are consistent with the trend for enhanced activation in the ASD group based on RFX analyses. These FFX findings are also consistent with results from the correlational analyses, which showed that ASD participants with more severe symptoms had higher activation in the bilateral IFG, which serves the cognitive evaluation of emotional voices.

The significant group differences observed under the FFX but not RFX model could be accounted for by the effects of increased statistical power in the former. Alternatively, group differences based on the FFX model could have been influenced by the potential presence of subgroups within the ASD cohort (rather than all 16 participants per se) who had relatively high parameter estimates in the regions listed above. This explanation assumes high variability of activation within the ASD group, which could have been due to range of factors, including differences in cognitive strategies and the degree of compensation used to recognise vocal affect bursts. However, a larger sample and revised study design are required to explore such subgroups, as discussed in more detail in the following section (Section 5.4.4).

Other possible sources of heterogeneity in the ASD group may include genetic and environmental risk factors (Lenroot & Yeung, 2013), or the presence of psychiatric comorbidities and the use of pharmacological intervention. Of note, up to 50% of participants with ASD were being treated for ADHD, anxiety or depression, although the type of pharmacological treatment was not consistent across these participants (e.g., a mix of dopamine agonist/antagonist, serotonin reuptake inhibitor, GABAergic agonic, beta blockers). To explore the potential effects of these factors, a post-hoc direct group comparison (with FFX analyses) of whole-brain activation was performed between ASD participants with and without

pharmacological treatment (n = 8 per group). ASD participants with treatment demonstrated significantly *lower* activation in bilateral visual areas and medial frontal regions (cluster-wise FWE-corrected threshold of $p < .05$, voxel-wise level of $p < .001$). This suggests that pharmacological effects were unlikely to contribute to the enhanced activation observed in the ASD group, but were nevertheless indicative of variability within the cohort

5.4.4. Exploring compensation for emotional voice processing in ASD

Although inferences about the FFX findings are limited only to the particular ASD and control cohorts assessed here, the enhanced activation observed in the ASD group may be useful for the generation of new hypotheses related to the neurobiology of ASD, such as those exploring mechanisms for compensation. Compensation for social impairments in ASD may account for the heterogeneity of symptom severity across individuals (Livingston & Happé, 2017; Ullman & Pullman, 2015). Since individuals with ASD often receive either formal or informal training to improve social communication, their ability to understand basic emotions may be learned and improved over time rather than being intuitive (Golan et al., 2010; Kouo & Egel, 2016). For example, they may use their strong "systemizing" skills (see Appendix B) to compensate for emotion recognition difficulties by adhering to knowledge of rules or patterns for recognising how and when emotions are typically expressed (e.g., Baron-Cohen, 2009; Golan et al., 2010). They may also rely on verbal reasoning to recognise emotions under testing conditions (Grossman, Bemis, Skwerer, & Tager-Flusberg, 2010), or cross-modal processing (e.g., relying on information from face-voice pairs) to compensate for emotion recognition difficulties experienced in a single modality (Vannetzel et al., 2011; Xavier et al., 2015).

To systematically explore the role of neurobiological compensation for vocal emotion recognition in ASD, future studies could include additional measures such as questionnaires or

interviews that query how each participant approached the task and the extent to which they found the task to be cognitively demanding (see Section 8.2.1. for a further discussion of these recommendations). Given a substantially larger sample, such measures may assist with identifying more homogenous subgroups of autistic individuals who share similar cognitive strategies to classify emotions in the voice. The neurobiological profiles of emotional voice processing in these subgroups may then be determined upon direct comparison to controls using RFX models, which may enable clearer inferences to be drawn about neural efficiency for emotional voice processing in ASD. This approach of assessing subgroups may ultimately allow the discovery of distinct neurobiological markers in ASD, which may have been otherwise concealed by high between-subject variance in brain activation potentially corresponding to differences in the use of cognitive strategies and compensatory effort across the participants tested.

Finally, it should be noted that compensation could have accounted for the discrepancy between the ASD group's performance (relative to controls) on neutral and emotional trials of the pre-scan task. While social skills training could have contributed to the ASD group's ability to classify basic emotions in vocal affect bursts at similar levels to controls, this would have had little benefit on their ability to classify neutral voices. Neutral voices, like those used here, do not often occur in natural settings (or training programs) and are more unfamiliar. They are ambiguous and not clearly defined by a social context. It is therefore possible that the ASD group did not have effective strategies for associating monotonous voices with neutrality, thus misattributing affective states to neutral voices.

5.4.5. Limitations

There were a number of limitations to this study, including the sample size, which was restricted to 16 participants per group due to the limited budget for MRI scanning. The small

sample size may have contributed to low power for detecting group differences on emotional trials of the pre-scan task (e.g., classification accuracy for basic emotions) and in brain activation under RFX analyses. The present sample size is largely typical of fMRI studies on ASD, as a meta-analysis of 90 fMRI studies revealed an average sample size of 12 participants with ASD (largest study consisting of 19 participants; Philip et al., 2012). However, it would be highly beneficial if future such studies could include a large enough sample size to enable potential sub-groups within the overall cohort to be explored (Thirion et al., 2007).

As aforementioned, the ASD group did not consist of individuals with "pure" ASD, since many participants had various psychiatric comorbidities for which they received a range of pharmacological treatments. Of note, high rates of depression, anxiety, and ADHD (55-85%) are reported in ASD (Joshi et al., 2010; Joshi et al., 2013), suggesting that the sample was still representative of the wider ASD population. Where possible, however, future fMRI studies should ideally enable examination of sub-groups of participants with more similar psychiatric profiles to limit sources of heterogeneity. In addition, participants with ASD were exclusively high-functioning, with a mean IQ in the high-average range, and were primarily in their teens to early 20s (with the exception of one middle-aged adult). It is recommended that future fMRI studies also examine the neural correlates of vocal affect burst recognition in individuals with lower intellectual function (matched to controls with low IQ) or young children who may be less capable of compensating for their social deficits.

Other limitations pertained to task design. On the pre-scan task, participants were allowed to listen to each stimulus as often as required, although the number of times they replayed the stimulus was not recorded. Groups were compared on percentage accuracy and intensity ratings alone, whereas additional measures like the extent of exposure to stimuli and reaction

time could have provided valuable information about subtle emotional voice processing difficulties in the ASD group (e.g., Ketelaars et al., 2016; Matsumoto et al., 2016). In addition, the classification accuracy for happy voices was at ceiling levels for the ASD (M = 100%) and control groups (M = 97.92%), suggesting little room for variation of scores. This was likely the case because all stimuli from the MAV battery (Belin et al., 2008) representing happiness were prototypes of laughter, which were highly distinguishable from stimuli representing the other basic emotions. Future studies could include other forms of vocal affect bursts representing happiness (e.g., mixing laughter with sighs of pleasure, which were often rated as representing "Happiness" instead of "Pleasure" in the original MAV study) to enable a wider distribution of accuracy scores and increase sensitivity for the detection of individual differences.

On the fMRI task, vocal affect bursts for all six basic emotions were presented within the same block, yielding brain activation that pertained to generalised emotional voice processing. It was therefore impossible to conduct post-hoc analyses to compare groups on emotion-specific activation, which would have been interesting, in light of research showing distinct neural networks for the perception of distinct emotions (Barrett & Wager, 2006; although see Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012 for evidence against a locationist approach). However, in order to acquire enough data to investigate the neural correlates of any particular emotion, a complete fMRI run would be required for each emotion of interest. Accordingly, this would take an unfeasible amount of time to complete if all the six emotions included here were to be investigated separately.

5.4.6. Conclusions

Behavioural findings from Study 1 indicated an emotional voice processing deficit in the ASD group, characterised by their tendency to misclassify neutral voices as being emotional at a higher rate than controls. RFX analyses of the fMRI data revealed that both groups recruited common task-relevant brain regions to classify vocal affect bursts, and showed no group differences in brain activation on direct comparison. In contrast, FFX analyses showed atypical, enhanced activation in the ASD group relative to controls across several regions, although these findings are limited to the present cohort of participants and cannot be generalised to the wider population of individuals with ASD. These findings may suggest the potential role of neurobiological compensation for emotional voice processing in ASD, which should be explored further using larger samples.

CHAPTER 6

Study 2: Behavioural and Brain Correlates of Emotional Voice Processing in the BAP in Relatives

Overview: Study 2 used the same behavioural and fMRI measures as Study 1 to examine the recognition of vocal affect bursts and their neurobiological substrates in family members of individuals with ASD who were determined to have BAP-positive status. It was hypothesised that relatives with the BAP would show a vocal emotion recognition deficit on the web-based (pre-scan) behavioural task compared to controls. It was also hypothesised that they would demonstrate atypical brain activation relative to controls when classifying vocal emotions in-scanner. The premise of this study is summarised in a brief introductory section, which includes relevant research from the literature review.

6.1. Introduction

Subtle autism-like features are expressed in approximately 20% of first-degree relatives of individuals with ASD at a milder intensity, not warranting a clinical diagnosis (Bolton et al., 1994; Constantino et al., 2010; Sasson, Lam, et al., 2013). Collectively known as the Broader Autism Phenotype (BAP), these characteristics suggest a genetic liability for ASD and are considered "endophenotypes" of ASD (Gerdts & Bernier, 2011; Geschwind, 2013; Piven, 2001; Sucksmith et al., 2011; see also Section 2.4.2).

Individuals with ASD have impairments in social cognition, including a reduced ability to interpret emotions expressed in the face and voice (Charbonneau et al., 2013; Harms et al., 2010; Heaton et al., 2012; Philip et al., 2010; Uljarevic & Hamilton, 2013). Similar deficits in emotion recognition have been identified in relatives of individuals with ASD (ASD-relatives), and represent behavioural components of the BAP. Within the face modality, parents and siblings demonstrate more difficulty than controls at identifying basic emotions (e.g., disgust, fear, happiness, sadness, surprise) as well as differentiating neutral expressions from emotional ones (Kadak et al., 2014; Palermo et al., 2006; Wallace et al., 2010; see also Section 3.4.4). They are also worse than controls at identifying complex emotions (e.g., pride, embarrassment) expressed in the eyes (Baron-Cohen & Hammer, 1997; Dorris et al., 2004). Further, fMRI studies have shown that compared to controls, individuals with ASD and first-degree relatives show lower activation in regions of the social brain (e.g., fusiform gyrus, STS, MTG, IFG, anterior cingulate cortex/ACC, medial prefrontal cortex/mPFC) when making implicit or explicit judgments about basic emotions in the face (Greimel et al., 2010; Spencer et al., 2011) or complex emotions in the eyes (Baron-Cohen, Ring, et al., 2006; Holt et al., 2014).

Within the voice modality, only two studies have assessed emotion recognition in ASD-relatives, both using stimuli which consist of prosody embedded in speech. One showed that siblings of individuals with ASD and comorbid ADHD were slower than controls at identifying basic emotions (specifically fear) in speech prosody, but faster than the individuals with ASD/ADHD themselves, thus demonstrating an intermediate level of ability (Oerlemans et al., 2014). The other showed that parents of individuals with ASD were less accurate than controls at identifying complex emotions in speech prosody (Tajmirriyahi et al., 2013). To date, however, no study has utilised non-linguistic forms of emotional vocalisations (i.e., vocal affect bursts like laughs, cries, screams) to investigate vocal emotion recognition in the BAP. Further, there has been no fMRI investigation of emotional voice processing in the BAP, whether using emotional speech prosody or vocal affect bursts. Vocal affect bursts are particularly valuable for vocal emotion research, since they are not subjected to the confounds of language processing and may therefore target emotion-specific networks in individuals with ASD and the BAP (Belin, Fillion-Bilodeau, et al., 2008; Scherer, 1994; see also Section 4.4).

The aims of the present study were to examine the behavioural and neurobiological correlates of emotional voice processing in ASD-relatives with the BAP, using the same behavioural (pre-scan) and fMRI paradigms of vocal affect burst recognition administered to participants with ASD in Study 1. It was hypothesised that compared to age- and IQ-matched controls, the BAP group would demonstrate poorer behavioural performance on the pre-scan task, showing lower recognition accuracy for vocal affect bursts representing the six basic emotions and a neutral category. It was also hypothesised that the BAP group would show atypical brain activation when classifying basic emotions in vocal affect bursts on the fMRI task.

6.2. Method

This project was approved by the Human Research Ethics Committee (HREC) at The Royal Children's Hospital Melbourne and the Human Research Ethics Advisory Group at The University of Melbourne. All participants provided written informed consent.

6.2.1. Participants

6.2.1.1. BAP group

The BAP group consisted of 13 adult relatives (6 males) of individuals with ASD who had been clinically diagnosed on DSM-IV or DSM-V criteria (American Psychiatric Association, 2000, 2013). They were recruited from nine multiplex families included for genetic research in the Collaborative Autism Study (CATS) conducted at The Royal Children's Hospital and The University of Melbourne (HREC#: 25043). Eleven were first-degree relatives of individuals with ASD (10 parents, 1 sibling), and two were second-degree relatives (1 grandparent, 1 first-cousin). Participants were aged between 19 and 64 years (M = 43.62, SD = 12.89). Each participant had a Full-Scale IQ in the *Average* range or above, except for one who fell in the *Low Average* range. Demographic information is summarised in Table 6.1. Two participants received medication for depression or anxiety, and none reported a history of neurological conditions. All were right-handed.

BAP status was assigned to all participants based on the presence of at least one of four behavioural markers of the BAP (i.e., being socially unaware, pedantic, aloof, and/or obsessive). This was determined by an extensive battery of qualitative and quantitative measures, administered as part of the detailed protocol for phenotyping family members included in the CATS (Trevis et al., 2019; see also Appendix H). Participants also provided self-ratings of BAP traits on the Broad Autism Phenotype Questionnaire (BAPQ; Hurley et al.,

2007). Nine scored above cut-off on at least one subscale (i.e., aloofness, pragmatic language difficulties, rigidity) based on norms derived from the continuous distribution of BAP traits across the general population (Sasson, Lam, et al., 2013).

6.2.1.2. Control group

Thirteen typically-developing adults (5 males) were recruited from the community through advertisements and word-of-mouth. They were matched with the BAP group on age and IQ (Table 6.1) and reported having no first- or second-degree relatives with ASD. They were screened for BAP traits using the BAPQ, all scoring below cut-off on each subscale based on the same general population norms (Sasson, Lam, et al., 2013). One participant received medication for anxiety. None had a history of neurological conditions. All were right-handed.

Table 6.1
Demographics for the BAP and Control Groups

	BAP	Controls
Sample Size (n)		
Females	7	8
Males	6	5
Age in years		
M (SD)	43.62 (12.89)	42.54 (11.85)
Range	19-64	22-60
Full-Scale IQ		
M (SD)	114.15 (12.23)	117.08 (7.98)
Range	88-130	109-137
Verbal IQ		
M (SD)	110.62 (13.21)	110.85 (9.70)
Range	93-131	97-128
Performance IQ		
M (SD)	114.23 (11.88)	119.38 (7.34)
Range	88-130	106-129

Note. Independent samples t-tests revealed no significant group differences for age, Full-Scale IQ, Verbal IQ, and Performance IQ ($p > .05$).

6.2.2. Experimental design

Two tasks were administered: (i) a behavioural task to assess vocal emotion recognition prior to the fMRI scan, and (ii) a similar task adapted for fMRI to elicit brain activation, as administered to individuals with ASD in Study 1. Methods were identical to those reported in Study 1 (see Section 5.2.2) and are therefore only described in brief here.

6.2.2.1. Pre-scan task

Participants performed a web-based task on vocal emotion recognition (Yap et al., 2018; see also Figure 5.1). The task incorporated 42 stimuli from the Montreal Affective Voices (MAV; Belin, Fillion-Bilodeau, et al., 2008), specifically vocal affect bursts for the six basic emotions (six stimuli per emotion) and monotonous, non-linguistic neutral vocalisations (six stimuli). On each trial, participants were required to classify a MAV stimulus into one of seven emotion categories (i.e., *Anger, Disgust, Fear, Happiness, Sadness, Surprise, No Emotion*) and rate its emotional intensity on a 7-point Likert-type scale (1 = *weak emotion* to 7 = *strong emotion*). An intensity rating of "0" was automatically assigned to all stimuli classified under *No Emotion*. There were 42 trials in total, yielding a maximum classification accuracy score of 42.

6.2.2.2. fMRI task

The fMRI task was designed using Presentation software (Version 16.3; Neurobehavioral Systems, 2013), and incorporated the same set of MAV stimuli from the pre-scan task. It comprised six "emotion" blocks, which alternated with six "baseline" (gender) blocks (see Figure 5.2). Six stimuli were presented in each block (i.e., six trials per block across a duration of 30 s). In an emotion block, participants were required to classify the vocal affect bursts using a forced-choice paradigm (e.g., happiness versus anger). Vocal affect bursts for all six

basic emotions were presented in the same block. In a baseline block, participants were required to classify the neutral vocalisations as male or female. The baseline blocks were designed to control for activation of no interest (e.g., associated with auditory, visual/lexical, motor processing) in the emotion blocks. Participants were instructed to respond as quickly and accurately as possible using a button response unit. Prior to scanning, participants performed practice trials on a computer consisting of other MAV stimuli (Belin, Fillion-Bilodeau, et al., 2008) that were not utilised in this study. They were also placed in a mock scanner to familiarize them with the MRI environment.

6.2.3. Image acquisition

Image acquisition parameters for fMRI data were identical to those from Study 1, as described fully in Section 5.2.3. A total of 120 EPI volumes per participant were acquired within a single run of the fMRI task (~6 min across 12 blocks).

6.2.4. Data analysis (fMRI)

The same methods described in Study 1 (Section 5.2.4) were used to pre-process and analyse the fMRI data via the Statistical Parametric Mapping software (SPM12, version 665; Wellcome Trust Centre for Neuroimaging, 2014). In brief, we used random- and fixed-effects models (RFX and FFX) to determine whole-brain activation within each group and to compare whole-brain activation between groups at a population and sample level, respectively. As described in detail in Section 5.2.4.2, RFX analyses have relatively low statistical power and account for between- and within-subject variability, whereas FFX analyses account for within-subject (scan-to-scan) variability alone (Karl J. Friston et al., 1999; Penny & Holmes, 2003). In this study, RFX analyses were performed on 13 contrast images across participants per group,

whereas FFX analyses were performed on the total number of EPI volumes across participants per group (i.e., 120 volumes x 13 participants per group).

As per Study 1, the design matrix for each participant contained a single regressor of interest (canonical HRF for emotion block), covariates of no interest (motion correction parameters), and a constant term (Figure 5.3). For RFX and FFX models, "emotion > baseline" T-contrasts were specified to determine activation within each group. For both models, T-contrasts for "BAP > controls" and "BAP < controls" were specified to determine whether the BAP group showed higher or lower activation from the "emotion > baseline" contrast relative to controls. Cluster-based thresholding was used to determine significant activation for each contrast at a family-wise error (FWE) corrected cluster-wise threshold of $p < .05$ (voxel-wise primary threshold of $p < .001$), unless specified otherwise. These thresholds were selected to match those defined in Study 1, in order to infer task replicability across the samples. As per Study 1, an explicit whole-brain mask (i.e., *mask_ICV.nii* from the SPM12 package, no threshold) was specified for all RFX and FFX group analyses. A high-pass filter was specified with a cut-off of 120 s to remove low-frequency signal variation

6.3. Results

6.3.1. Classification of vocal affect bursts and neutral voices on the pre-scan task

Behavioural performance on the pre-scan task showed that classification accuracy for neutral voices did not differ between the BAP group and controls (Figure 6.1), $t(24) = 0.50$, $p = .62$, $d = 0.20$. Both groups also demonstrated similar total classification accuracy rates of approximately 77% for vocal affect bursts, collapsed across the six basic emotions (BAP: $M = 76.50\%$, $SD = 11.09$; Controls: $M = 77.56\%$, $SD = 6.94$). A two-way mixed ANOVA revealed no interaction between group and each basic emotion category on classification accuracy

(Figure 6.2a), $F(3.18, 76.21) = 1.55$, $p = .21$, $\eta^2 = 0.06$, and no main effect for group, $F(1, 24) = 0.09$, $p = .77$, $\eta^2 = 0.00$. There was a main effect for basic emotion category, $F(3.18, 76.21) = 17.78$, $p = .00$, $\eta^2 = 0.42$. Bonferroni-corrected post-hoc comparisons revealed that across both groups, classification accuracy for happiness and sadness was significantly higher than all other emotions ($p < .001$), and accuracy for disgust was significantly higher than anger and fear ($p < .01$), but not surprise. Anger accuracy was significantly lower for the BAP group (Figure 6.2a), $t(24) = 2.39$, $p = .03$, $d = 0.94$, although this effect was no longer significant after Bonferroni correction ($\alpha = .008$), possibly due to the small sample size.

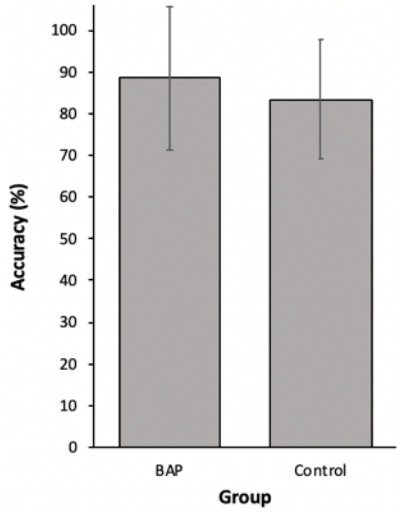


Figure 6.1. Group mean performance on the pre-scan task for the classification of neutral voices. Error bars represent 95% confidence intervals.

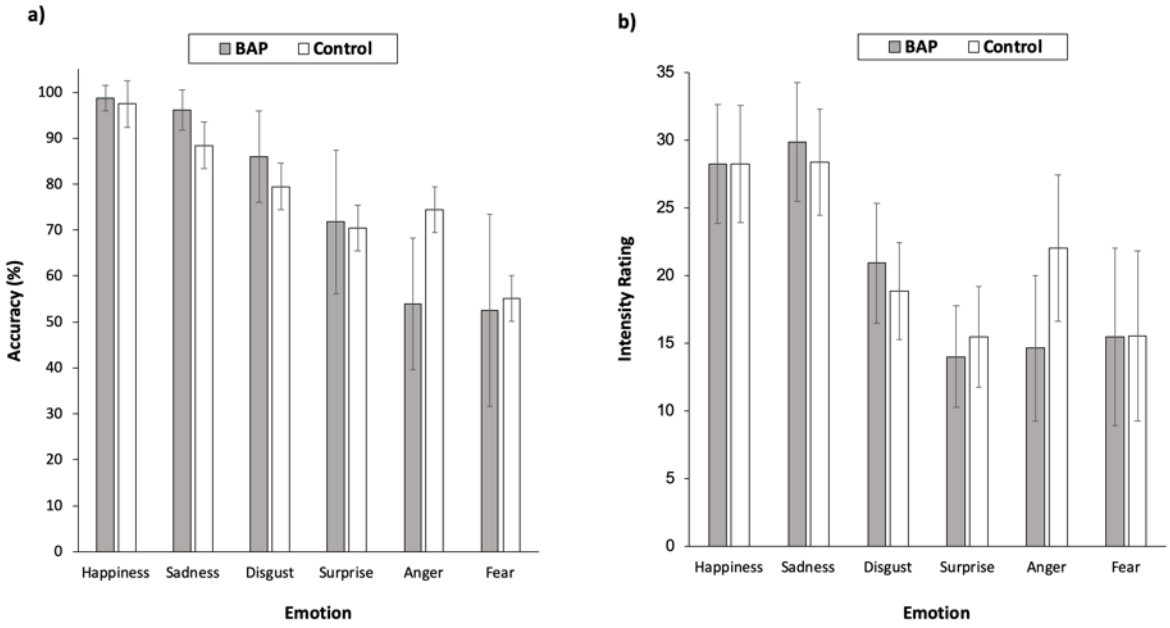


Figure 6.2. Group mean performance on the pre-scan task for (a) emotion classification accuracy and (b) emotion intensity for vocal affect bursts of each basic emotion category. Error bars represent 95% confidence intervals.

Analyses were also performed for mean emotional intensity ratings of vocal affect bursts that were accurately classified (Figure 6.2b). Like classification accuracy, we found no interaction effect between group and basic emotion category on emotional intensity ratings, $F(3.09, 74.06) = 1.55$, $p = .21$, $\eta^2 = 0.06$. There was no main effect for group, $F(1, 24) = 0.24$, $p = .63$, $\eta^2 = 0.01$, although there was a main effect for basic emotion category $F(3.09, 74.06) = 20.81$, $p = .00$, $\eta^2 = 0.46$. Bonferroni-corrected post-hoc comparisons revealed that across both groups, intensity ratings for happiness and sadness were significantly higher than all other emotions ($p \leq .001$), and accuracy for disgust was significantly higher than surprise alone ($p \leq .001$). The intensity rating for anger was significantly lower for the BAP group (Figure 6.2b), $t(24) = 2.11$, $p = .045$, $d = 0.83$, although this effect was no longer significant after Bonferroni correction ($\alpha = .008$). Within each group, intensity ratings for each basic emotion correlated positively with

classification accuracy for that emotion [BAP: $r(11) = .61$ to $.97$, $p \leq .05$; Controls: $r(11) = .59$ to $.93$, $p \leq .01$], with the exception of happiness in both groups and sadness in the BAP group.

6.3.2. fMRI of vocal affect burst recognition

6.3.2.1. fMRI task performance

The BAP and control groups demonstrated high performances on the emotion and baseline blocks of the fMRI task (Figure 6.3a), indicating that the corresponding brain activation was reliable. A two-way mixed ANOVA revealed no significant interaction effect between group and block on classification accuracy, $F(1, 24) = 2.81$, $p = .11$, $\eta^2 = 0.11$, and no main effect for group, $F(1, 24) = 0.69$, $p = .41$, $\eta^2 = 0.03$. There was a main effect for block, $F(1, 24) = 8.02$, $p = .01$, $\eta^2 = 0.25$, with higher accuracy on the baseline versus emotion block across both groups. Reaction time was also assessed for correct trials of the emotion and baseline blocks (Figure 6.3b). There was no significant interaction between group and block type on reaction time, $F(1, 24) = 1.50$, $p = .23$, $\eta^2 = 0.06$, and no main effect for group, $F(1, 24) = 0.11$, $p = .75$, $\eta^2 = 0.004$. There was a main effect for block type, $F(1, 24) = 61.46$, $p = .00$, $\eta^2 = 0.72$, with faster reaction time on correct baseline versus emotion trials for both groups.

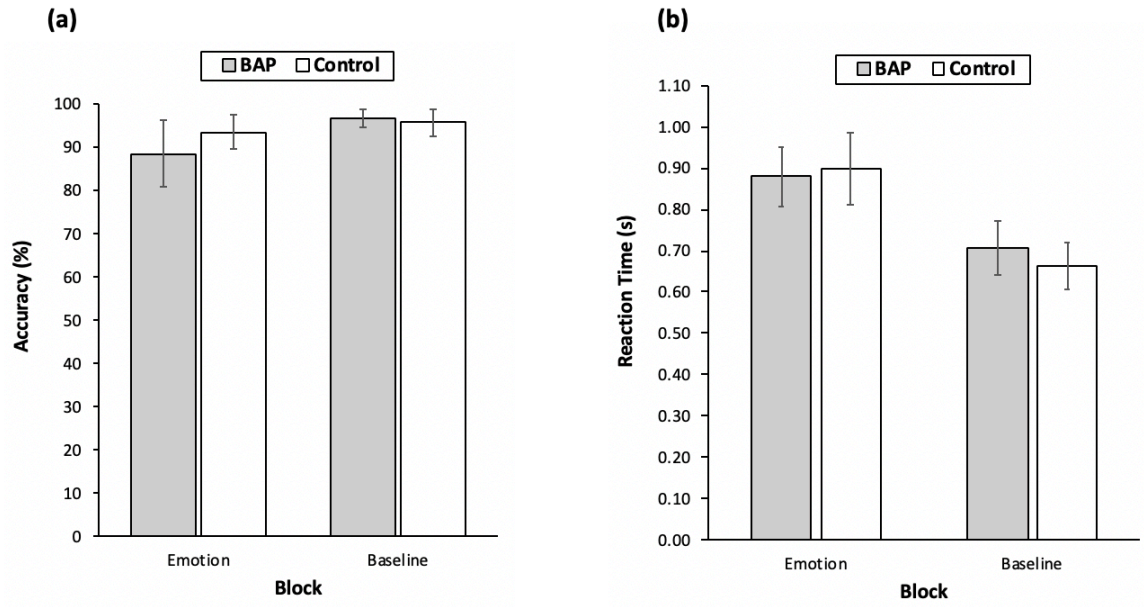


Figure 6.3. Group mean performance on the fMRI task for (a) classification accuracy on the emotion and baseline blocks, and (b) reaction time (on correct trials) for each block. Error bars represent 95% confidence intervals.

6.3.2.2. fMRI analysis

6.3.2.2.1. Whole-brain analyses (RFX): activation within BAP and control groups

Whole-brain RFX analyses revealed six significant clusters of activation in the BAP group ($k \geq 69$) and five in the control group ($k \geq 154$). Functional maps of the significant clusters within each group are shown in Figure 6.4, and MNI coordinates of local maxima (peak voxels) per cluster are listed in Table 6.2. Regions of significant activation that were common to both groups include the SMA, middle cingulate cortex (MCC), and the bilateral IFG (pars triangularis and opercularis), anterior insula, orbitofrontal cortex (OFC; IFG pars orbitalis), fusiform gyrus, and middle frontal gyrus (DLPFC). Both groups also showed significant activation in the left superior and inferior parietal gyri, left inferior temporal gyrus, and bilateral cerebelli. The BAP group activated the superior temporal poles bilaterally, whereas activation was left-lateralised in the control group. The control group activated the precentral gyri bilaterally, whereas activation was left-lateralised in the BAP group. Occipital activation was distributed bilaterally in controls (e.g., primary visual area/calcarine sulcus, lateral occipital

gyri, lingual gyri), whereas activation in some of these regions (e.g., calcarine sulcus, superior and middle occipital gyri) was left-lateralised in the BAP group. Importantly, however, none of these group differences were significant on direct comparison of groups based on RFX analyses (see Section 6.3.2.2.2).

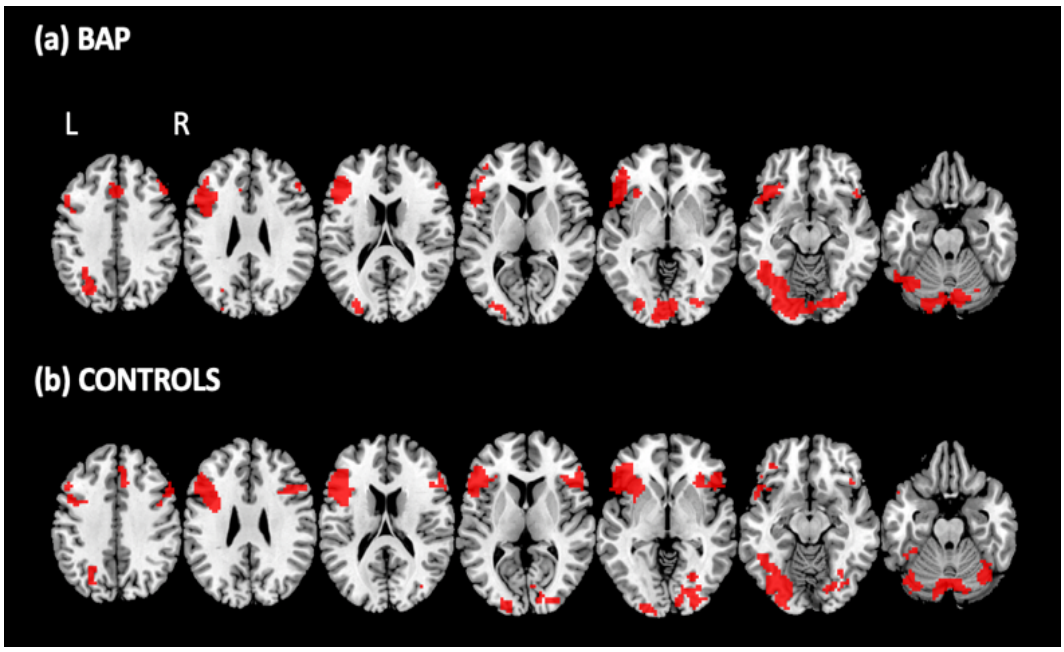


Figure 6.4. Clusters of significant activation from the RFX analyses of the "emotion > baseline" T-contrast in the (a) BAP group and (b) control group at a cluster-wise FWE-corrected threshold of $p < .05$ (voxel-wise primary threshold of $p < .001$). Activation images are shown overlaid on axial T1-weighted images in MNI template space. Note that both groups demonstrated significant activation in the right OFC (IFG pars orbitalis) and anterior insula, although activation in these regions are only visible on these axial slices for controls. L = left; R = right.

Table 6.2

Whole-Brain RFX Analyses: Peak Voxels from Significant Clusters within the BAP and Control Groups

	Local maxima				
Cluster Size (*k*)	Region	*x*	*y*	*z*	T-score
BAP					
1500	L fusiform gyrus	-27	-70	-7	10.81
	L calcarine sulcus	-3	-91	-4	8.02
	L cerebellum (VI)	-39	-67	-22	7.33
	R fusiform gyrus	30	-79	-13	7.15
	L cerebellum (Cr I)	-21	-85	-22	6.95
	R cerebellum (Cr I)	9	-79	-28	6.69
	L lingual gyrus	-6	-79	-7	6.63
	L inferior occipital gyrus	-21	-88	-7	6.46
	L middle occipital gyrus	-30	-88	23	5.82
867	L inferior frontal gyrus (orbitalis)	-48	17	-10	10.7
	L inferior frontal gyrus (opercularis)	-45	17	32	9.71
	L inferior frontal gyrus (triangularis)	-45	41	-1	8.85
	L middle frontal gyrus	-45	38	23	6.6
	L superior temporal pole	-57	14	-1	5.95
160	L inferior parietal gyrus	-27	-70	41	6.79
88	R middle frontal gyrus	48	29	38	5.64
	R inferior frontal gyrus (triangularis)	54	32	14	5.47
79	L superior frontal gyrus (medial)	0	26	38	4.76
	L supplementary motor area	-3	14	50	4.10
	L anterior cingulum	-9	26	26	3.97
69	R inferior frontal gyrus (orbitalis)	48	23	-16	6.49
	R insula				
		39	26	-7	6.26
Controls					
1338	R lingual gyrus	24	-67	-1	9.05
	L fusiform gyrus	-36	-73	-19	8.61
	R cerebellum (VI)	9	-73	-22	7.34
	L cerebellum (Cr I)	-6	-73	-25	7.17
	R fusiform gyrus	33	-67	-19	6.93
	L inferior occipital gyrus	-21	-100	-7	6.54
	R cerebellum (VIIb)	18	-76	-43	6.38
	L middle occipital gyrus	-18	-100	-1	6.18
	R middle occipital gyrus	33	-91	2	6.16
	L cerebellum (VIIb)	-6	-76	-40	6.1
1111	L inferior frontal gyrus (triangularis)	-57	20	17	8.24
	L inferior frontal gyrus (opercularis)	-36	5	26	8.04
	L insula	-39	17	-4	7.98
	L superior temporal pole	-54	11	-16	7.42
	L inferior frontal gyrus (orbitalis)	-54	23	-7	6.43
422	R inferior frontal gyrus (triangularis)	54	23	2	7.23
	R insula	33	29	-4	7.17

Cluster Size (*k*)	Local maxima Region	*x*	*y*	*z*	T-score
	R inferior frontal gyrus (orbitalis)	39	29	-7	7.11
	R inferior frontal gyrus (opercularis)	57	17	38	6.18
	R middle frontal gyrus	48	11	47	5.17
	R precentral gyrus	45	5	41	4.76
233	R superior frontal gyrus (medial)	9	32	44	7.10
	L supplementary motor area	-6	17	53	5.98
	R supplementary motor area	9	14	71	5.36
	L superior frontal gyrus (medial)	-9	23	41	4.12
154	L superior parietal gyrus	-24	-64	47	8.31
	L inferior parietal gyrus	-33	-55	47	5.76
	L middle occipital gyrus	-27	-70	38	5.39

Note. Results are from the "emotion > baseline" T-contrast, thresholded at a cluster-wise FWE-corrected level of $p < .05$ (voxel-wise primary threshold of $p < .001$). The table shows cluster size (*k*), along with MNI coordinates and T-scores from the three highest peak voxels from each structure within the cluster. Peak voxels are separated by more than 8 mm. Peak voxels are labelled according to the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). L = left; R = right.

6.3.2.2.2. Whole-brain analyses (RFX): direct comparison between groups

Whole-brain RFX analyses revealed no significant clusters of activation when the two groups were directly compared (i.e., "BAP > controls" and "BAP < controls" contrasts). These findings suggest that significant group differences in brain activation underlying the recognition of vocal affect bursts cannot be inferred at the population level. A trend for group differences only emerged at a voxel-wise uncorrected threshold level of $p < .001$, for the "BAP > controls" contrast. Specifically, the BAP group showed a trend for greater activity in the left fusiform gyrus, calcarine sulcus, and middle occipital gyrus (see Table I.1 in Appendix I for MNI coordinates of peak voxels). Given that the RFX analyses had low statistical power, activation within and between these specific cohorts of BAP and control participants were explored further using whole-brain FFX analyses (FFX analyses were also performed on the ASD and control groups' fMRI data in Study 1 for similar reasons; see Chapter 5).

6.3.2.2.3. Whole-brain analyses (FFX): activation within groups and direct comparison between groups

Whole-brain FFX analyses revealed eight significant clusters of activation in the BAP group ($k \geq 39$) and 11 in the control group ($k \geq 28$) at a stringent FWE-corrected cluster threshold of $p < .05$ (voxel-wise primary threshold of $p < .0001$). Functional maps of the significant clusters within each group are shown in Figure 6.5, and MNI coordinates of local maxima per cluster are listed in Table J.1 in Appendix J. The FFX analyses yielded several regions of significant activation that were common to the BAP and control groups, many of which were also found in both groups under RFX analyses (Section 6.3.2.2.1). Additional regions that were common to both groups include the left STS/MTG and the bilateral precentral gyri, middle frontal gyri, angular gyri, superior and inferior parietal gyri, and occipital gyri (superior, middle, and inferior). Activation in the right STS (extending adjacent STG and MTG) was significant in the control group alone, although between-groups FFX analyses revealed no significant differences in activation for this region.

For the direct comparison of activation between groups, whole-brain FFX analyses revealed no significant clusters for the contrast of "BAP < controls" at an FWE-corrected cluster threshold of $p < .05$ (voxel-wise primary threshold of $p < .001$). However, significant group differences were found for the opposite contrast of "BAP > controls" (Figure 6.5c). Specifically, the BAP group demonstrated significantly higher activation than controls in one cluster ($k = 142$) within the left lateral occipital cortex, with peak voxels at the superior occipital gyrus [-18 -85, 38], $T = 3.77$, and middle occipital gyrus [-39, -79, 32], $T = 4.26$. Overall, the FFX analysis of the "BAP > Controls" contrast suggests that significant group differences can be inferred at the sample level, despite the RFX analysis showing no evidence of significant group differences which can be inferred at the population level.

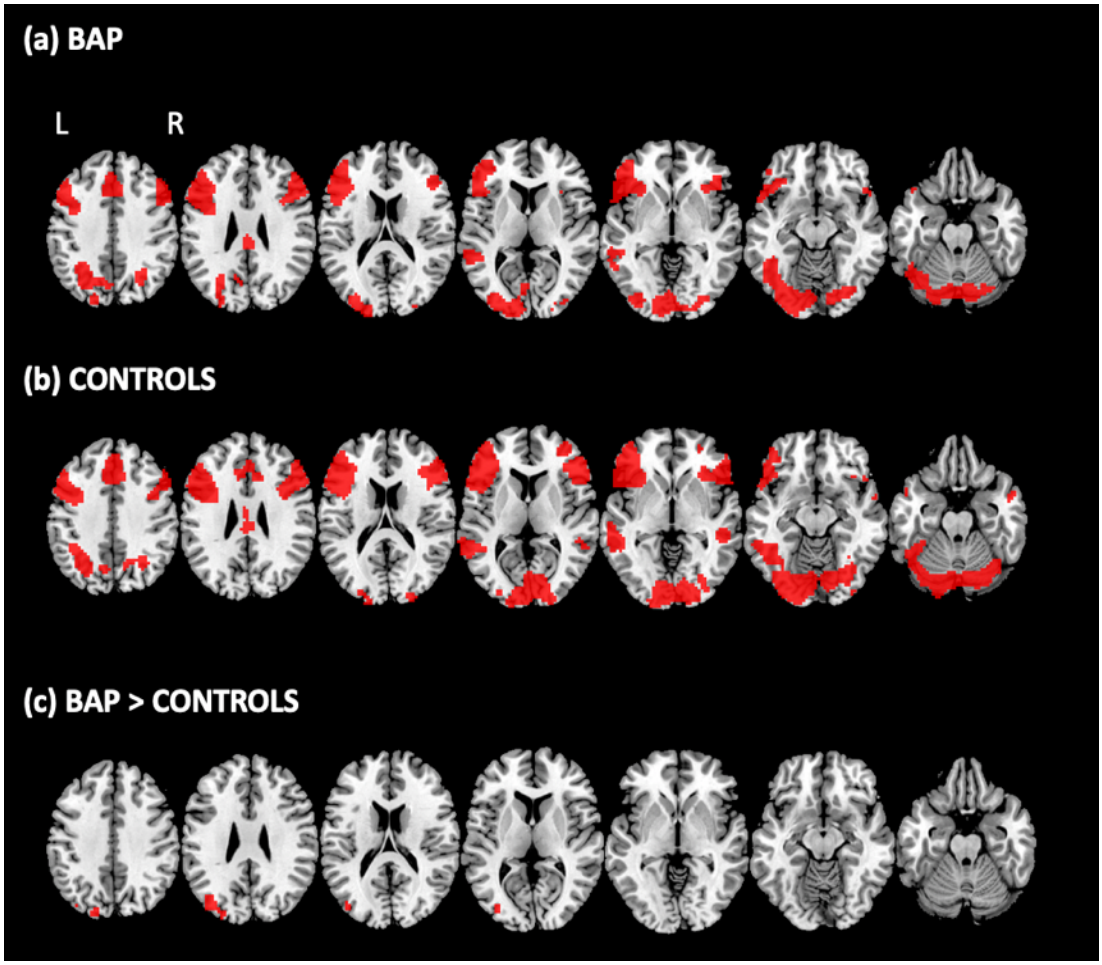


Figure 6.5. Clusters of significant activation from the FFX analyses of the "emotion > baseline" T-contrast in the (a) BAP group and (b) control group at a cluster-wise FWE-corrected threshold of $p < .05$ (voxel-wise primary threshold of $p < .0001$). This figure also shows (c) clusters of significantly higher whole-brain activation in the BAP group relative to controls at a cluster-wise FWE-corrected threshold of $p < .05$ (voxel-wise primary threshold of $p < .001$). Activation images are shown overlaid on axial T1-weighted images in MNI template space. L = left; R = right.

6.4. Discussion

Study 2 assessed behavioural performance and brain activation associated with the recognition of vocal affect bursts in ASD-relatives with the BAP. The BAP group classified vocal affect bursts of the six basic emotions and neutral voices at similar rates to controls. The two groups engaged similar brain regions to classify basic emotions in-scanner. RFX analyses revealed no significant differences in brain activation between groups, although FFX analyses revealed enhanced activation in left occipital regions for the BAP group relative to controls.

Importantly, inferences pertaining to the FFX findings are only valid for the specific cohort of ASD-relatives (n = 13) assessed here, and should not be generalised to the wider population of ASD-relatives with the BAP.

6.4.1. Vocal emotion recognition in the BAP

In contrast to the first hypothesis, behavioural findings on the pre-scan task revealed no vocal emotion recognition deficit in the BAP group. Findings on the pre-scan task were also inconsistent with studies showing impaired recognition of basic and complex emotions in speech prosody for ASD-relatives compared to controls (Oerlemans et al., 2014; Tajmirriyahi et al., 2013). It is possible that group differences emerged on those studies, but not in the present one, because emotional cues in speech prosody are generally more difficult to identify than in vocal affect bursts (Hawk et al., 2009; Heaton et al., 2012). To process emotional prosody, participants have to disregard the content of speech (e.g., linguistic and semantic components) and focus on emotional cues alone (e.g., paralinguistic components), which is more cognitively demanding than for non-linguistic vocal expressions and therefore, likely prone to error. Further, the study by Oerlemans et al. (2014) assessed the recognition of basic emotions exclusively in siblings of children with ASD plus comorbid ADHD (i.e., not "pure" ASD), suggesting that factors specific to ADHD could have also contributed to their lower performance compared to controls.

Additionally, it is possible that the BAP and control groups had similar, low levels of alexithymia, which could have contributed to the lack of significant group differences in vocal emotion recognition ability. This assumption is drawn from studies showing that lower scores on self-report measures of alexithymia (i.e., poor awareness or understanding of one's own emotions) correlate with better emotion recognition across modalities of expression (e.g., both

face and voice) in typically-developing individuals and individuals with ASD (Cook et al., 2013; Heaton et al., 2012). Future studies should therefore include additional measures to account for the role of alexithymia on the recognition of vocal affect bursts in the ASD-relatives with the BAP.

In addition, the sample size in this study was small, potentially contributing to low statistical power for detecting significant group differences (see Section 6.4.5. for a further discussion). Accordingly, replication of these behavioural findings should be assessed using a substantially larger sample of ASD-relatives with the BAP. It would be particularly interesting to determine whether the trends for poorer classification accuracy and emotional intensity rating of angry vocal affect bursts observed in the BAP group (i.e., no longer significant under Bonferroni-correction for multiple comparisons) would reach statistical significance with a larger sample.

It should be noted that in Study 1, the ASD group showed a vocal emotion recognition deficit on the same pre-scan task, where they misclassified neutral voices as being emotional at a higher rate than controls. It was reasoned that the ASD group were perhaps less efficient at using compensatory strategies to associate monotonous voices with neutrality. This is a reasonable assumption, since individuals with ASD are less likely to receive training to recognise the absence of affective states in neutral expressions, as opposed to the presence of specific affective states in emotional ones (see Section 5.4.4). Here, the BAP group was able to differentiate neutral voices from emotional ones at comparable rates to controls, suggesting that the deficit observed in the ASD group is unlikely to qualify as a potential endophenotypic marker of the BAP.

6.4.2. Neural correlates of vocal emotion recognition in the BAP and controls

The BAP and control groups performed the fMRI task at ceiling levels, indicating that their brain activation reflects correct task performance, rather than guessing. RFX and FFX analyses of the fMRI data revealed significant activation in task-relevant regions common to both groups. Only findings from the RFX analyses will be discussed in this section (unless otherwise specified), since they can be generalised to the wider population of ASD-relatives with the BAP and typically-developing controls.

Under the RFX model, the BAP and control groups engaged similar regions to perform the task, including those that serve social cognition (e.g., bilateral IFG, anterior insula, OFC, MCC, and left superior temporal pole). The anterior insula and MCC were likely involved with salience detection here (Menon, 2015), although they have also been implicated in empathy (Fan et al., 2011; see also Section 3.3.2). Notably, the IFG is crucial for the cognitive evaluation of emotional voices (Frühholz & Grandjean, 2013; Schirmer & Kotz, 2006). Neither group demonstrated significant activation in emotional voice areas within the temporal lobe (e.g., STS and adjacent MTG and STG; Ethofer et al., 2012; Schirmer & Kotz, 2006). However, activation in the STS (left-lateralised for BAP and bilateral for controls) was observed using FFX analyses. While this discrepancy could reflect higher statistical power available in the FFX model, it could also suggest that activation in the STS was highly variable within each group, and hence could not be extended to the wider population as a whole (as required under the RFX model).

RFX analyses revealed that the BAP and control groups also activated regions associated with attention (e.g., inferior and superior parietal gyri), motor planning and motor control (e.g., SMA, precentral gyrus), and visual processing (e.g., fusiform gyrus and occipital structures),

as well as the cerebellum. These findings suggest that both groups may have engaged in some degree of cross-modal integration (e.g., mental imagery) and the auditory-motor "mirroring" of affective states (e.g., preparation of orofacial gestures that correspond to vocal expressions; Warren et al., 2006) to identify basic emotions in vocal affect bursts.

It is interesting to note that some regions activated by the BAP group were also activated by the ASD group under the RFX model in Study 1, which employed the same fMRI task. These include the bilateral IFG (pars opercularis and triangularis), left fusiform gyrus, and cerebellum, which were incidentally also activated by the control groups from Study 1 and the present study. These regions therefore appear to be central to the recognition of vocal affect bursts, with robust activation that can be inferred across different populations, regardless of their ASD or BAP status.

6.4.3. Atypical brain activation specific to the BAP cohort in this study

Here, RFX analyses comparing the activation between the BAP and control groups yielded no significant group differences in any brain region, indicating no evidence for atypical brain activation that can be inferred in the wider population of ASD-relatives with the BAP. Only a trend for enhanced activation emerged in the left fusiform gyrus and left occipital regions for the BAP group at an uncorrected significance threshold. Consistent with this trend, FFX analyses revealed that the BAP group had significantly higher activation than controls in a single cluster within the left lateral occipital cortex (i.e., superior and middle occipital gyri). However, the atypical brain activation resulting from FFX analyses can only be inferred for this specific cohort of 13 BAP participants relative to controls, and cannot be generalised to the population as a whole.

It is possible that significant group differences emerged under the FFX but not RFX model due to increased statistical power in the former. Alternatively, it is possible that the FFX analysis alone yielded significant group differences due to the presence of potential subgroups within the BAP cohort (rather than all 13 participants per se) who had relatively high parameter estimates in the left lateral occipital cortex. This explanation assumes high variability of activation within the BAP group, which could have been influenced by heterogeneity in their use of cognitive strategies to perform the task, possibly including a strong reliance on visual-based strategies for some. Enhanced activation in the peripheral visual areas could also suggest that subgroups of participants required increased auditory attention to perform the task (e.g., Cate et al., 2009; Maeder et al., 2001), since emotional voice areas within the temporal lobe are structurally connected to the ipsilateral occipital cortex (Ethofer et al., 2012). In addition, variability of activation within the BAP group could have been influenced by heterogeneity of participant characteristics (e.g., different types of relatives with multiple behavioural markers of the BAP), as discussed in more detail with limitations of the study in Section 6.4.5.

6.4.4. Exploring potential neurobiological endophenotypes of ASD

Overall, the FFX findings of enhanced brain activation specific to this cohort of ASD-relatives may inform the generation of new hypotheses investigating the role of neurobiological compensation for emotional voice processing in ASD-relatives with the BAP. These hypotheses should be investigated at the population level using substantially larger samples that would enable the exploration of neurobiological profiles for potential subgroups of ASD-relatives, such as those who share similar cognitive strategies to approach the task (as per the recommendations for future ASD studies presented in Section 5.4.4).

It should be noted that similar inferences and implications for future research were drawn from the findings of group differences under the FFX model in Study 1, which showed significantly higher brain activation in the ASD group compared to controls. Like the BAP group assessed here, the ASD group demonstrated significantly higher activation relative to controls in the left lateral occipital cortex (i.e., superior and middle occipital gyri). However, enhanced brain activation in the ASD group was not confined to these regions, but was distributed bilaterally across more extensive occipital regions (e.g., calcarine sulcus, lingual gyrus, cuneus) and regions associated with emotional voice processing (e.g., IFG, STS), memory retrieval (e.g., hippocampus, parahippocampal gyrus), executive function (e.g., middle frontal gyrus, cerebellum), and motor and somatosensory processing (e.g., precentral and postcentral gyri).

Accordingly, the profile of atypical brain activation specific to the BAP cohort assessed here appears to be similar, but less extensive, than that observed in the ASD cohort assessed in Study 1. It may be possible that the BAP group demonstrated a milder expression of neurobiological compensation for emotional voice processing than the ASD group, characterised by enhanced activation in left peripheral visual areas alone. This assumption hints at the presence of potential endophenotypic markers of ASD, which should be ascertained at the population level with an improved study design. Of note, inferences about similarities and differences between the ASD and BAP groups were based only on indirect measures (e.g., how "alike" each group compared to their respective control groups). A direct comparison of the two groups was not performed in this thesis due to a large age disparity between them (i.e., ASD: 23.00 years ± 10.20; BAP: 43.62 years ± 12.89), and the two groups were therefore assessed in separate studies and compared to different groups of controls to whom they were matched on age. Future studies exploring hypotheses related to neurobiological endophenotypes of emotional voice processing should therefore include larger samples of age-

matched ASD and BAP groups (inclusive of more homogenous, identifiable subgroups), as well as controls, to allow the direct comparison of brain activation across groups.

6.4.5. Limitations

Limitations pertaining to task design for the pre-scan and fMRI paradigms in the present study are similar to those addressed in Study 1 (Section 5.4.5). Regarding sample size, the BAP and control groups only consisted of 13 participants each, due to the limited budget for MRI scanning. This small sample size may have contributed to low statistical power for detecting group differences in behavioural performance on the pre-scan task and brain activation under RFX analyses. As aforementioned, future studies should include larger samples that would enable the exploration of potential subgroups of ASD-relatives with the BAP.

Composition of the BAP group was also mixed, comprising a majority of parents and smaller numbers of siblings and second-degree relatives from different multiplex families. This suggests heterogeneity in the relative recurrence risk of ASD and genetic or environmental risk factors (Sandin et al., 2014). Given the large majority of parents, the BAP group mainly consisted of middle- to older-aged adults, who could have acquired strategies to compensate for any difficulties with social functioning over the years. Therefore, it would be interesting for future studies to exclusively assess a younger cohort of ASD-relatives (e.g., siblings in childhood or early adolescence) with the BAP who may be less capable of compensating for social difficulties. Of note, the BAP group was not age-matched to the younger ASD group in Study 1, and both groups were therefore not directly compared. Accordingly, interpretations of similarities/differences between the two groups were limited only to indirect measures.

The ASD-relatives had a mixture of at least one of four behavioural BAP markers (i.e., being socially unaware, pedantic, aloof, and/or obsessive), as determined on an extensive protocol

for phenotyping family members included the CATS (Appendix H). The majority had multiple behavioural markers (e.g., a combination of three or four markers), and it may be the case that each behavioural marker was associated with a distinct neurobiological profile, which could not be differentiated in this study. Nonetheless, the sample was constrained only to a group of ASD-relatives with BAP-positive status, which was in itself an attempt to minimise heterogeneity, as many previous studies assessing social cognition in relatives did not account for whether or not the sample met categorical criteria for the BAP (see Ingersoll & Wainer, 2014; Sucksmith et al., 2011).

6.4.6. Conclusions

Behavioural findings from Study 2 indicated intact vocal emotion recognition abilities in the ASD-relatives with the BAP relative to controls. RFX analyses of the fMRI data revealed that both groups recruited common task-relevant brain regions to classify vocal affect bursts, and showed no group differences in brain activation on direct comparison. In contrast, FFX analyses showed atypical, enhanced activation in the BAP group within the left lateral occipital cortex, although this finding is limited to the present cohort of participants and cannot be generalised to the wider population of ASD-relatives with the BAP. These findings may inform the generation of new hypotheses exploring potential endophenotypic markers of ASD, characterised by similarities in the profile of neurobiological compensation for emotional voice processing in individuals with ASD and relatives with the BAP.

CHAPTER 7

Study 3: Emotional Voice Processing and BAP Traits in the General Population

Overview: Study 3 examined the correlation between the recognition of vocal affect bursts and self-ratings of BAP traits in the general population of individuals without a family history of ASD. The same web-based behavioural task from Studies 1 and 2 was used to measure emotion recognition accuracy and intensity ratings for vocal affect bursts. Participants provided self-ratings on the BAPQ, which includes three subscales assessing different domains of the BAP (i.e., aloofness, pragmatic language difficulties, rigidity). It was hypothesised that higher self-ratings on each BAPQ subscale would correlate with lower recognition accuracy and emotional intensity ratings for vocal affect bursts. The research conducted in Study 3 was published as an empirical study in the *Journal of Autism and Developmental Disorders*, and the published manuscript is presented in this chapter.

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Note. Electronic supplementary material were published with the online version of this manuscript. They are referred to as "Online Resource 1" and "Online Resource 2" in the manuscript, and included in this thesis under Appendix K.

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ORIGINAL PAPER

Enhanced Sensitivity to Angry Voices in People with Features of the Broader Autism Phenotype

Valerie M. Z. Yap[1] · Neil M. McLachlan[1] · Ingrid E. Scheffer[2,3] · Sarah J. Wilson[1]

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Abstract
The present study examined whether the ability to recognize vocal emotional expressions is negatively related to features of the Broader Autism Phenotype (BAP) in the general population. We assessed 61 typically developing adults on a BAP self-report measure (Broader Autism Phenotype Questionnaire) and a purpose-developed online emotion recognition task for efficient delivery of non-linguistic vocal stimuli corresponding to the six basic emotions. Contrary to expectations, we found that higher self-ratings of rigid BAP traits correlated with better recognition accuracy and higher intensity ratings for angry voices. We interpret this anger-specific association as an advantage for enhanced threat detection in the BAP and discuss this finding in the broader context of personality research and interpersonal theory.

Keywords Broader Autism Phenotype · Emotion recognition · Vocal affect bursts · Anger · Threat sensitivity · Rigidity

Introduction

Autism Spectrum Disorder (ASD) is a pervasive neurodevelopmental condition characterized by two primary symptom domains of deficits in social communication and fixated interests or repetitive behaviours (American Psychiatric Association 2013). Individuals with ASD are often reported to have reduced social cognition and empathy (Baron-Cohen 2001; Baron-Cohen and Wheelwright 2004), which include difficulties with recognizing the emotions of others (Harms et al. 2010; Lindner and Rosen 2006; Philip et al. 2010). In this study, we examined whether emotion recognition difficulties are also associated with subclinical characteristics of ASD in the general population, known as the Broader Autism Phenotype (BAP). We based our assessment on the recognition of emotional vocal expressions, particularly non-linguistic expressions that are not confounded by properties of speech.

The Broader Autism Phenotype

The BAP describes a group of behavioural and personality characteristics that are milder expressions of ASD features (Sucksmith et al. 2011). Unlike ASD, however, the BAP is not considered a clinical disorder, as any functional difficulties do not cause significant impairment in daily life (Gerdts and Bernier 2011). BAP features have been documented in approximately 20–40% of family members of individuals with ASD, providing strong evidence for a genetic liability to the disorder (Bolton et al. 1994; Constantino et al. 2010; Gamliel et al. 2009; Georgiades et al. 2013; Gerdts and Bernier 2011; Sasson et al. 2013b). Further, family studies have reported that the BAP is more prevalent in monozygotic (77–92%) than dizygotic (10%) twins (Bailey et al. 1995; Le Couteur et al. 1996), first-degree than more distant relatives (Pickles et al. 2000), and multiplex compared to single-incidence families (Gerdts et al. 2013; Losh et al. 2008; Virkud et al. 2009).

The BAP has been examined beyond the context of heritability in ASD families, with studies reporting that milder ASD-like characteristics are also distributed within the

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✉ Sarah J. Wilson
sarahw@unimelb.edu.au

[1] Melbourne School of Psychological Sciences, The University of Melbourne, Parkville, VIC 3010, Australia

[2] Departments of Medicine and Paediatrics, The University of Melbourne, Austin Health, Heidelberg, VIC 3084, Australia

[3] Department of Neurology, The Royal Children's Hospital, Parkville, VIC 3052, Australia

general population (Constantino and Todd 2003; Hoekstra et al. 2007). Assessment of BAP features in population-based samples include self- and informant-report questionnaires, of which the Autism Spectrum Quotient (AQ; Baron-Cohen et al. 2001), Social Responsiveness Scale (SRS; Constantino and Gruber 2005), and Broad Autism Phenotype Questionnaire (BAPQ; Hurley et al. 2007) are most common. Of note, an exploratory factor analysis of scales from these questionnaires revealed three primary dimensions of the BAP in the general population: aloofness, pragmatic language difficulties, and rigidity (Wainer et al. 2011). The aloof dimension covers reduced social awareness or interests, while the pragmatic language dimension covers poor understanding or inappropriate means of communication within a social context. The rigid dimension covers resistance to change or reduced behavioural and cognitive flexibility. Overall, these BAP dimensions correspond to the three key domains of impairment in ASD (i.e., social interaction difficulties, communication deficits, and stereotyped repetitive interests or behaviors) defined by former DSM-IV diagnostic criteria (American Psychiatric Association 2000).

Individuals from the general population who score higher on BAP measures may experience a range of interpersonal difficulties, including poor friendship history (i.e., reduced interest in making friends, fewer friends, shorter duration of friendships), increased loneliness, lower empathy, anxious or avoidant romantic attachment style, and higher frequency of being bullied (Jamil et al. 2017; Jobe and White 2007; Kunihira et al. 2006; Lamport and Turner 2014). Individuals with aloof traits are also more likely to form satisfying relationships with other aloof individuals (e.g., friends, college roommates), but not with warmer, more socially engaged individuals (Faso et al. 2016).

Emotion Recognition in the BAP

The ability to identify and understand the emotional cues of others is important for effective social communication, presenting an interesting but fairly novel area for BAP research in the general population. At present, research is largely confined to the study of facial expressions. Poljac et al. (2012) reported that college students with higher AQ scores were worse at identifying facial expressions representing the basic emotions of anger, disgust, and sadness. The high-AQ scorers were also less sensitive to milder or more subtle expressions of these emotions and relied on more intense facial displays for accurate identification. Another study with college students found that higher BAPQ scores (specifically for aloofness and pragmatic language difficulties) and poorer social skills on a role-playing measure correlated with lower recognition accuracy for milder facial expressions, but not for more intense expressions (Sasson et al. 2013c). Sasson et al. (2013), however, did not specify whether the correlations applied to a composite recognition score across the emotions assessed (i.e., happy, sad, angry, fearful, and neutral faces) or to specific emotions. Of note, these findings are consistent with clinical studies showing reduced facial emotion recognition in individuals with ASD (Harms et al. 2010) and their family members (Kadak et al. 2014; Palermo et al. 2006).

More research is warranted to examine whether BAP traits in the general population are associated with the recognition of emotions expressed through modalities other than the face. The voice, in particular, carries crucial information about an individual's affective state that can be discerned by a listener even when the individual is out of immediate view (Johnstone and Scherer 2000). Studies have found that individuals from the general population can identify emotions in speech prosody at accuracy rates well above chance (55–65%), drawing from acoustic cues in the voice like fundamental frequency, speech rate, intensity, and voice quality (Banse and Scherer 1996; Johnstone and Scherer 2000; Scherer 2003). Clinical research has shown that this ability is compromised in ASD (Golan et al. 2007; Lindner and Rosen 2006; Philip et al. 2010; Rutherford et al. 2002), although evidence for an impairment is not always consistent, likely due to methodological differences across studies (Baker et al. 2010; Grossman et al. 2010). It is not surprising that affected individuals may have difficulty understanding emotional cues in the voice, since other socio-emotional difficulties like theory of mind deficits (Baron-Cohen 2001), reduced empathy (Baron-Cohen and Wheelwright 2004), and alexithymia (Bird and Cook 2013) are often reported in ASD. Research has also shown that parents of children with ASD demonstrate poorer performance on "mind reading in the voice" (theory of mind task), which included the recognition of complex emotions in speech prosody (Tajmirriyahi et al. 2013).

Using a sample of college students, Ingersoll (2010) examined whether BAP features in the general population are more broadly associated with "nonverbal sensitivity" across modalities of emotional expressions, including faces, body postures, and speech prosody. Using the AQ, they found that self-ratings of poorer social skills and greater attention to detail/patterns correlated with poorer recognition of emotional faces, specifically sadness and anger (but not happiness and fear). In contrast, AQ scores did not correlate with the recognition of specific emotions in body postures and speech prosody. These results suggest that poor emotion recognition ability associated with BAP traits in the general population is not generalized across modalities, but specific to facial expressions. However, Ingersoll (2010) suggested that correlations were found exclusively for the recognition of facial emotions because the task was easy for most participants and significantly simpler than the recognition of postures and speech prosody.

It is worth considering whether the use of alternate BAP measures and emotional stimuli would yield findings that support a link between BAP traits and vocal emotion recognition ability in the general population. While Ingersoll (2010) used the AQ to measure BAP traits in her sample, a more recent study found that the BAPQ has better psychometric properties for assessing the BAP in the general population (Ingersoll et al. 2011). Compared to the AQ, the BAPQ has higher internal consistency, higher criterion validity (to outcome measures of mood/anxiety symptoms and personality traits), and a replicable factor structure corresponding to the three theoretical dimensions of the BAP (i.e., aloofness, pragmatic language difficulties, rigidity; Ingersoll et al. 2011). Further, the BAPQ was originally developed to determine milder characteristics of the BAP in parents of children with ASD (Hurley et al. 2007), unlike the AQ which was developed to identify high-functioning individuals with a clinical diagnosis of ASD (Baron-Cohen and Wheelwright 2004).

As for vocal stimuli, although most emotion recognition studies (within and outside the ASD context) have employed speech prosody, valuable information about an individual's affective state is also communicated through non-linguistic vocalizations or vocal "affect bursts" (Belin et al. 2008; Hawk et al. 2009; Schröder 2003; Simon-Thomas et al. 2009). Vocal affect bursts include laughter, screams, cries, sighs, and groans. Compared to speech prosody, affect bursts are considered to be less culturally dependent, more raw or reflexive, and hence, more accurate representations of affective states that are not confounded by linguistic content (Belin et al. 2008; Hawk et al. 2009). They are generally easier to recognize, with accuracy rates ranging from 68 to 81% (Belin et al. 2008; Schröder 2003). They also have evolutionary significance, with some occurring early in development before language and speech are acquired (e.g., infants crying to communicate with their mother; Zeifman 2001).

Present Study

As yet, research has not been conducted to assess whether poorer recognition of vocal affect bursts constitute a marker of the BAP in the general population. This is significant if we are to accurately understand the full spectrum of performance in milder phenotypes of ASD. We examined correlations between self-ratings on the BAPQ and recognition accuracy for vocal affect bursts representing the six basic emotions (i.e., anger, disgust, fear, happiness, sadness, and surprise) in a non-clinical sample who have no family members with ASD. In addition, we assessed whether levels of BAP traits were associated with intensity ratings of vocal affect bursts (i.e., how "strong" participants perceived the emotions to be). Intensity is a common dimension of physiological arousal in emotion research (Juslin and Laukka 2001; Laukka et al. 2005) and served as an additional measure of sensitivity to emotional stimuli in our study.

Based on prior research on social difficulties in ASD and the BAP, we hypothesized that higher scores on each BAPQ scale measuring the three primary BAP dimensions (i.e., aloofness, pragmatic language difficulties, and rigidity) would correlate with lower recognition accuracy and lower intensity ratings for vocal affect bursts from each basic emotion category. To test these hypotheses, we developed a new online program for assessing recognition and intensity ratings for a selection of validated stimuli from the Montreal Affective Voices (MAV) battery of vocal affect bursts (Belin et al. 2008).

Method

This project was approved by the Human Ethics Advisory Group at The University of Melbourne.

Participants

Sixty-three fluent English speakers (35 females) were recruited from the community by word-of-mouth and advertisements. This sample size was determined to achieve 81% power at an alpha level of 0.05 for correlation coefficients of at least moderate effect size ($r > .35$) using a web-based sample size calculator (StatsToDo; Chang 2014). One male participant was excluded from the analysis due to malfunctioning of the computer software at the time of testing. Eight participants reported being previously diagnosed with a psychiatric condition ($n = 4$ with depression, $n = 3$ with anxiety, $n = 1$ with comorbid depression and anxiety), of which only three reported ongoing symptoms. No significant mean differences were found across all performance measures between participants with and without a psychiatric history. However, the male participant with comorbid depression and anxiety was excluded from the analysis, as he was an outlier in our performance measure of vocal emotion recognition (i.e., scored below three standard deviations of the mean on recognition accuracy for angry and sad voices). Characteristics of the 61 remaining participants are shown in Table 1. No participant reported having ASD or family members diagnosed with ASD.

Materials

Montreal Affective Voices (MAV)

The MAV is a validated set of non-linguistic vocal affect bursts designed for cross-cultural research on auditory emotional processing (Belin et al. 2008). MAV stimuli were recorded by ten different actors (five females) under

Table 1 Characteristics of the sample ($N = 61$)

Age	
Range	18–70
M	30.56
SD	11.34
Full-scale IQ[a]	
Range	100–140
M	119.15
SD	8.97
Educational background	
Postgraduate (Masters/PhD)	60.7%
Undergraduate (Bachelor)	37.7%
Year 12	1.6%
Nationality	
Australian	47.5%
Asian	36.0%
Other[b]	16.4%

[a]General intellectual functioning was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler 1999)

[b]Participants of various European, African, Middle Eastern, North American, and South American nationalities were also included

instruction to produce short emotional interjections across a range of emotion categories using the vowel ah (/a/). The original set of MAV stimuli consists of 90 vocalizations corresponding to eight emotion categories of anger, disgust, fear, happiness, sadness, surprise, pleasure, pain, and a neutral category (no emotion). To minimize task duration, we selected a subset of 42 vocalizations that corresponded to the six basic emotions (anger, disgust, fear, sadness, surprise, happiness) and the neutral category, with three male and three female vocalizations per category. For each category, we refined our selection to vocalizations that sounded the most similar based on consensus judgments between authors (e.g., angry voices with a distinguishable growl and roughness, disgusted voices with a distinguishable rise in pitch contour corresponding to the interjection "eugh").

Emotion Recognition Task

The emotion recognition task uses novel online software that we purposely designed for efficient and randomized delivery of MAV stimuli (Yap et al. 2013). The program includes a purpose-built graphic interface that allows participants to hear each stimulus as often as required before rating it in terms of its emotion category and degree of intensity (Fig. 1). Correct classification of emotions involved a seven-alternative forced choice task (six basic emotions and neutral category), and intensity ratings were made on a 7-point Likert-type scale (1 = *weak emotion* to 7 = *strong emotion*). An intensity rating of 0 was expected for trials of the neutral

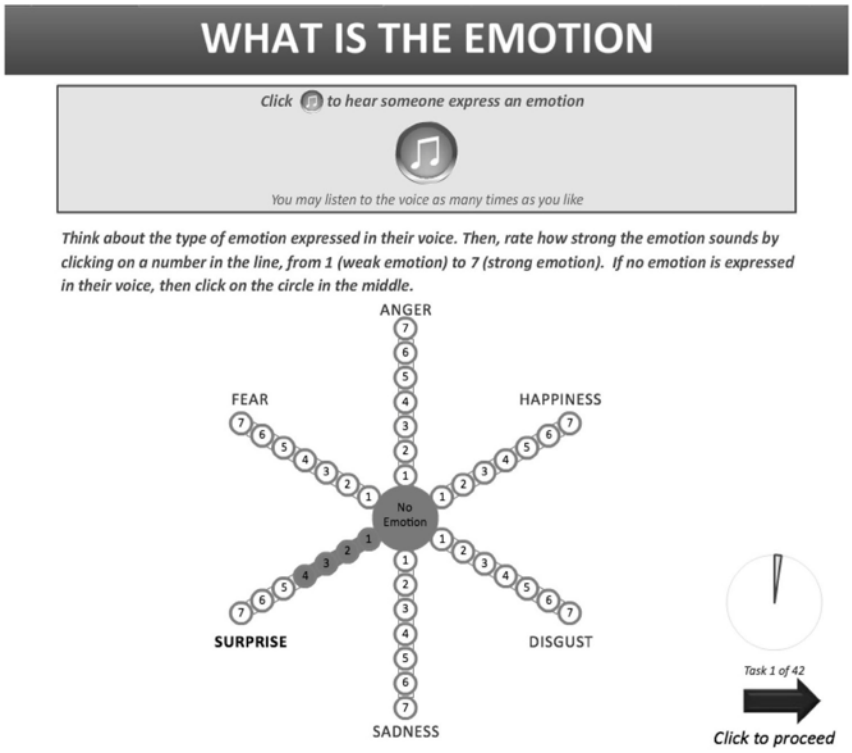


Fig. 1 Graphic interface of a trial from the online emotion recognition task. In this trial, the emotion category of surprise and intensity rating of four were selected in response to a MAV stimulus. The location of each basic emotion category was randomized around the neutral category after every seven trials

category. There were 42 trials in total, corresponding to a maximum total emotion recognition accuracy score of 42 points. Responses were stored in an XML data file located on a secure online server and downloaded for subsequent analyses.

Broad Autism Phenotype Questionnaire (BAPQ)

The BAPQ is a 36-item self-report questionnaire designed to measure features of the BAP that correspond with milder impairments of ASD (Hurley et al. 2007). The BAPQ has three 12-item scales: (a) aloof personality (e.g., "I prefer to be alone rather than with others"), (b) pragmatic language (e.g., "I can tell when someone is not interested in what I am saying"), and (c) rigid (e.g., "I have a hard time dealing with changes in my routine"). All scales have high internal reliability, with alpha coefficients ranging from 0.85 to 0.94 (Hurley et al. 2007). Participants rate how often each item applies to them on a 6-point Likert-type scale (1 = *very rarely* to 6 = *very often*).

Procedure

All participants provided signed informed consent. The emotion recognition task and BAPQ were presented in a counterbalanced order across participants. Participants completed the emotion recognition task on a computer in a soundproof room at The University of Melbourne, with stimuli presented through an external speaker adjusted to a comfortable listening volume. Participants also completed a brief health screen about their medical and psychiatric history, and an assessment of general intellectual functioning using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler 1999).

Results

Data were analysed using IBM SPSS Statistics (Version 21.0). The distribution of each variable was assessed for normality according to z-scores of the skewness value ($z < 2.58$). Variables that were not normally distributed were subjected to the Log10 or arcsine transformation (Sokal and Rohlf 1995). All transformed data were subsequently checked for normality. For ease of interpretation, parametric tests on the untransformed (original) data are reported whenever the transformed (normalized) data yielded similar results. Parametric tests of the original data are also reported in place of non-parametric tests (performed on original data that remained skewed even after transformation) when results were similar across both analyses.

Descriptive Statistics

Emotion Recognition Accuracy

The mean total recognition accuracy across all seven categories of the emotion recognition task was 81.36% ($SD = 7.03$). Figure 2 shows the recognition accuracy for each basic emotion category. Overall, our findings compare favorably with those from Belin et al. (2008) original study on the validation of MAV stimuli, with the clear exception of happiness which showed the highest accuracy scores in our study (98%; ceiling effect) but lowest in Belin et al.'s study (60%). The lower recognition accuracy for happiness reported by Belin et al. can be attributed to its confusion with the category of "pleasure", which was included as a forced-choice alternative. Accordingly, Belin et al. suggested that pleasure be excluded as a response option in future MAV-related studies, as we have done here. Similarities between recognition accuracy rates from our study and Belin et al.'s (2008) suggest that our purpose-built online task and abbreviated choice of MAV stimuli are valid for research on vocal emotion recognition.

In our study, voices of fear and surprise were most often confused, with approximately 20% of fearful voices mistaken to represent surprise and vice versa. Confusion between fear and surprise was also reported by Belin et al. (2008) as well as others studying vocal emotion recognition (Pell et al. 2008; Simon-Thomas et al. 2009). Voices representing the six basic emotions were rarely confused with the neutral category (1% of all trials), indicating that participants did not show a response bias for the central response option on our graphical interface (Fig. 1), but rather, actively engaged in the task. Two participants reported post-hoc that they did not know the neutral category was a response option, and we therefore excluded them from all analyses involving the neutral category (including analyses of total recognition accuracy).

Belin et al. (2008) reported gender effects for the recognition of MAV stimuli, with females performing better than males. In our study, a two-way mixed ANOVA revealed no interaction between gender and emotion category for accuracy, $F(3.33, 196.53) = 0.65$, $p = .60$, $\eta_p^2 = 0.01$, indicating that recognition ability across the six emotion categories was not significantly different for males and females (see Online Resource 1 for gender-specific means). There was also no main effect of gender on recognition accuracy, $F(1, 59) = 2.20$, $p = .14$, $\eta_p^2 = 0.04$. However, there was a main effect of emotion category, $F(3.33, 196.53) = 28.73$, $p < .001$, $\eta_p^2 = 0.33$. Bonferroni-corrected post-hoc analyses indicated that participants were more accurate at identifying happy and sad voices compared to other emotions ($p < .001$, $d = 0.92–1.84$), although accuracy was lower for sad compared to happy voices ($p < .001$, $d = 0.81$). No significant

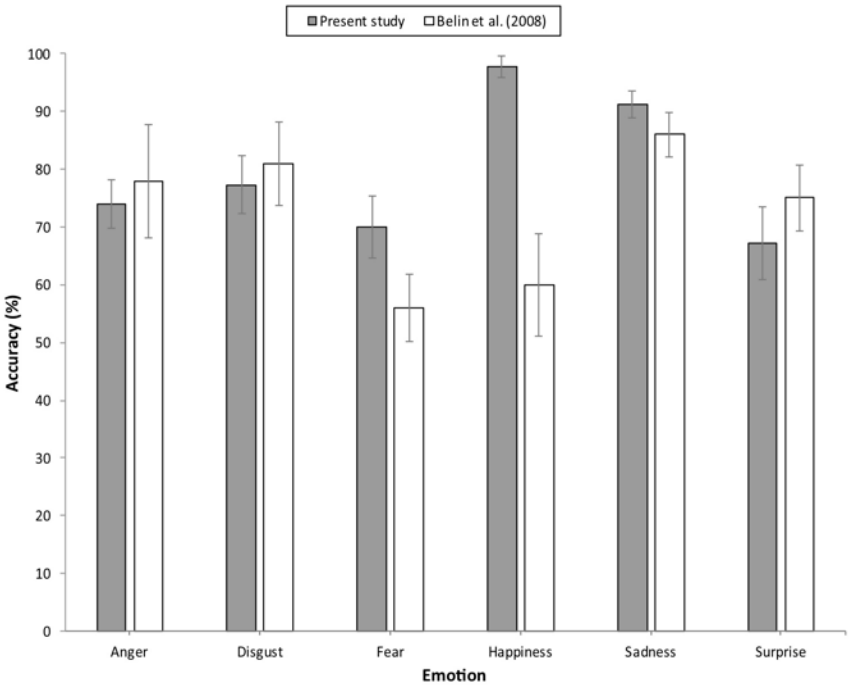


Fig. 2 Mean recognition accuracy for each emotion category from the present study ($N=61$) and Belin et al.'s (2008) original study on the validation of MAV stimuli ($N=30$). In Belin et al. (2008), means were reported with standard errors, which were converted to 95% confidence intervals represented by error bars in this figure

differences in accuracy were found among voices of disgust, anger, fear, and surprise ($p=.78–1.00$).

Emotion Intensity Ratings

The mean total intensity rating across all six basic emotion categories of the emotion recognition task was 137.42 ($SD=25.20$), out of a possible maximum total of 252 points. Figure 3 shows intensity ratings for each basic emotion category. A two-way mixed ANOVA revealed no interaction between gender and emotion category on intensity ratings, $F(4.53, 267.09)=0.38$, $p=.85$, $\eta_p^2=0.01$ (see Online Resource 1 for gender-specific means). We also found no main effect of gender on intensity ratings, $F(1, 59)=0.06$, $p=.82$, $\eta_p^2=0.001$. However, we found a main effect of emotion category, $F(3.33, 196.53)=28.73$, $p<.001$, $\eta_p^2=0.33$. Bonferroni-corrected post-hoc analyses indicated that participants rated voices of happiness and sadness to be stronger than all other emotions ($p<.001$, $d=0.82–2.30$), whereas voices of surprise were rated to be of the weakest intensity ($p<.001$, $d=0.96–2.30$).

BAPQ

The mean total BAPQ score was 2.52 points ($SD=0.52$). Descriptive statistics for self-ratings of the three primary BAP components are reported in Fig. 4 (see Online Resource 2 for a distribution of scores per BAPQ scale). Scores on the BAPQ are similar to those reported in other studies assessing the general population (Ingersoll et al. 2011; Sasson et al. 2013a), with the exception of rigid scores, which are lower in our study. Research on the general population has also shown that females have lower scores on the BAPQ, particularly on the aloof and pragmatic language scales (Ingersoll 2010). However, a two-way mixed ANOVA revealed no interaction effect between gender and scores on BAPQ scales, $F(2, 118)=1.20$, $p=.30$, $\eta_p^2=0.02$ (see Online Resource 1 for gender-specific means). Further, there were no main effects of gender, $F(1, 59)=0.37$, $p=.55$, $\eta_p^2=0.01$, and scale, $F(2, 118)=1.85$, $p=1.62$, $\eta_p^2=0.03$, on BAPQ scores.

Correlational Analyses

Emotion Recognition Accuracy and the BAP

Bivariate correlations between emotion recognition accuracy and self-ratings of BAP features are shown in Table 2. We found that better recognition of angry voices was associated with higher scores on the Rigid scale of the BAPQ, $r(59)=0.32$, $p=.013$, with a medium effect size. This finding is counter to our hypothesis that participants with higher levels of BAP traits would be poorer at recognizing vocal emotions. No significant correlations were found for the remaining emotion categories and BAPQ scales (including

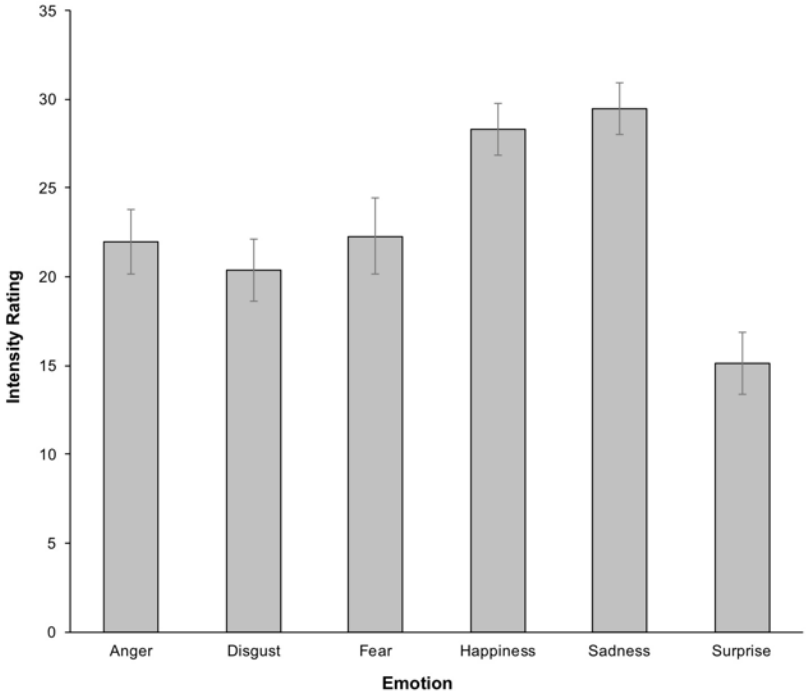


Fig. 3 Mean intensity ratings for vocal affect bursts representing the six basic emotions. (maximum score per emotion = 42 points). Error bars represent 95% confidence intervals

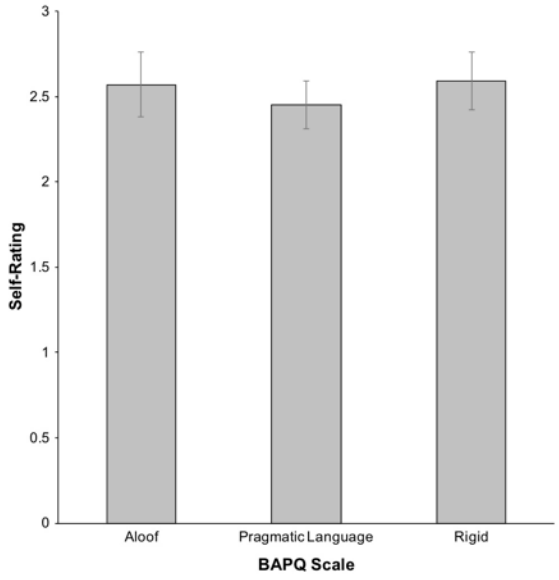


Fig. 4 Mean self-ratings of BAP features on scales of the BAPQ (maximum score per scale = 6 points). Error bars represent 95% confidence intervals

Table 2 Correlations between emotion recognition accuracy and BAPQ scores

Emotion category	BAPQ scales			
	Total	Aloof	Pragmatic language	Rigid
Total	0.078	0.053	0.011	0.124
Anger	0.214	0.215	−0.043	0.315*
Disgust	0.040	−0.011	0.140	−0.014
Fear	−0.095	−0.026	−0.152	−0.071
Happiness	−0.044	−0.088	−0.104	0.084
Sadness	−0.113	−0.085	−0.038	−0.146
Surprise	0.065	0.035	0.076	0.056

Pearson's *r* product-moment correlation coefficients are reported here
*$p < .05$

BAPQ total score), suggesting specific effects of rigid BAP traits on the recognition of angry voices.

Emotion Intensity Ratings and the BAP

Bivariate correlations between emotion intensity ratings and self-ratings of BAP features are shown in Table 3. We found a correlation with small effect size between higher intensity ratings for anger and higher BAPQ rigid scores, $r(59) = 0.29$, $p = .024$. No significant correlations were found for the remaining emotion categories and BAPQ scales (including

Table 3 Correlations between emotion intensity ratings and BAPQ scores

Emotion category	BAPQ scales			
	Total	Aloof	Pragmatic language	Rigid
Total	0.033	−0.043	−0.023	0.154
Anger	0.192	0.179	−0.027	0.289*
Disgust	0.087	−0.031	0.173	0.097
Fear	−0.072	−0.064	−0.099	−0.013
Happiness	0.049	−0.030	−0.055	0.204
Sadness	−0.101	−0.154	−0.110	0.031
Surprise	0.022	−0.096	0.070	0.000

Pearson's *r* product-moment correlation coefficients are reported here
*$p < .05$

BAPQ total score). This finding is consistent with the specific association found between better recognition of angry voices and higher rigid BAP traits.

Emotion Recognition Accuracy and Intensity Ratings

We found positive bivariate correlations between recognition accuracy and intensity ratings for each emotion category, suggesting that the ability to identify vocal emotions was associated with how intense the emotions were perceived to be, as also reported by other researchers (Juslin and Laukka 2001). Specifically, accuracy-intensity correlations with strong effect sizes were found for surprise, disgust, anger, and fear, $r(59) = 0.74–0.91$, $p < .001$, while correlations of medium effect sizes were found for happiness and sadness, $r(59) = 0.35$, $p < .001$.

Discussion

We examined whether self-ratings of BAP features in the general population are associated with recognition accuracy for non-linguistic vocal expressions representing the six basic emotions. We hypothesized that higher self-ratings on the three primary BAP dimensions would be associated with lower recognition accuracy of vocal affect bursts. Contrary to expectations, correlational analyses revealed that higher self-ratings of rigid personality traits were associated with better recognition of angry voices. Higher self-ratings of rigidity were also associated with higher intensity ratings for angry voices, suggesting a robust association between rigid features of the BAP and sensitivity to anger. Of note, no significant correlations (positive or negative) were found between other BAP features and recognition accuracy or intensity ratings for any of the other basic emotions.

BAP Features Do Not Impair the Recognition of Vocal Affect Bursts

Our findings suggest that individuals from the general population with more BAP features are not at a disadvantage for understanding vocal affect bursts. As such, difficulties with vocal affect burst recognition do not constitute a marker of the BAP, at least in people who have no family members with ASD. These findings were unexpected in light of clinical studies reporting reduced emotion recognition ability across modalities in ASD (Harms et al. 2010; Lindner and Rosen 2006; Philip et al. 2010). It is worth noting that some clinical studies have shown that individuals with ASD can recognize basic emotions in speech prosody as accurately as controls (Baker et al. 2010; Grossman et al. 2010), but are worse at recognizing more complex vocal emotions related to theory of mind processes (Golan et al. 2007; Rutherford et al. 2002). In a similar vein, perhaps the lack of significant negative correlations between BAP traits and vocal emotion recognition in our study reflects our use of non-linguistic stimuli (Belin et al. 2008), which resemble prototypical expressions of emotions that are generally easy to recognize and do not require much cognitive interpretation.

Enhanced Sensitivity to Angry Voices in the BAP

Using our vocal emotion recognition paradigm, we unexpectedly found positive correlations between anger-specific processing and rigid features of the BAP in the general population. Since anger is a negative-valence emotion associated with appraisals of dominance and threat, our key findings suggest that individuals who have more rigid BAP traits are particularly sensitive to threatening information in the voice. It is interesting that we found no correlations between BAP traits and the recognition of fear, another threat-related emotion. Anger and fear can be distinguished according to their motivational tendencies, whereby anger elicits approach-related behaviour while fear evokes avoidance-related behaviour (Carver and Harmon-Jones 2009). Angry signals often arise from the source of threat itself and can be used to assert social dominance, whereas fearful signals often reflect an awareness of threat which may result in submission or the goal to protect oneself (Bossuyt et al. 2014).

The accurate identification of angry expressions appears to have an evolutionary advantage, as indicated by facial emotion research on the "anger superiority effect", where angry faces are recognized more quickly and accurately than happy or friendly (non-threatening) faces when both are presented in visual search tasks (Hansen and Hansen 1988; Öhman et al. 2001). The anger superiority effect has also been reported in high-functioning ASD (Ashwin et al. 2006; Isomura et al. 2014; Rosset et al. 2011), implying that individuals with atypical social development have intact

mechanisms for detecting threat, although they may rely on different strategies to do so (e.g., feature-based versus holistic processing of angry faces).

While behavioural paradigms assessing the anger superiority effect have not been adapted for auditory emotion research, an attentional bias towards angry voices can be inferred from neuroimaging studies in the general population. Specifically, studies have found enhanced activity to angry prosody in voice-selective areas (e.g., superior temporal sulcus) and regions involved with reflexive processing of salient stimuli (e.g., the amygdala), even when task demands do not require selective attention to the voice (Grandjean 2005; Sander et al. 2005). However, studies have yet to examine whether individuals with ASD have similar neural responses to angry voices that allow them to process threatening information more efficiently.

Personality, Interpersonal Styles, and Threat Detection in the BAP

Support for sensitivity to threat in individuals with higher levels of rigid BAP traits may be drawn from the broader context of personality research. The "Big-Five" (McCrae and John 1992) personality trait of neuroticism has been linked with rigidity of thought and behaviour on the AQ and BAPQ (Austin 2005; Wainer et al. 2011; Wakabayashi et al. 2006). Of note, neuroticism is associated with psychological distress, high trait anxiety, attentional bias to unpleasant emotional information and a greater tendency to appraise daily experiences as being negative (Costa and McCrae 1980; Gomez et al. 2002; Tong 2010; Watson and Clark 1984). Individuals with higher levels of neuroticism and trait anxiety are also more prone to interpret ambiguous stimuli or situations as being threatening and avoid such encounters (Bar-Haim et al. 2007; Calvo and Castillo 2001; Lommen et al. 2010). In addition to neuroticism, higher self-ratings of rigid traits on the BAPQ also correlate with higher rates of anxiety and obsessive-compulsiveness in the general population (Wainer et al. 2011). It is therefore possible that underlying interactions between neuroticism and anxiety in our sample may at least partially account for the anger-specific association with rigid BAP features found here.

Although rigidity is not typically discussed in terms of its social relevance, its relationship with enhanced sensitivity to threat may have consequences for social functioning in the BAP. According to interpersonal theory, successful relationships depend on the extent to which individuals are able to engage in complementary social behaviour along two dimensions of dominance/submission and affiliation/hostility (Carson 1969; Kiesler 1983; Leary 1957). Complementary interpersonal styles are considered to be opposite on dominance but similar on affiliation, whereby for example, dominant behaviour is likely to elicit a submissive response (and vice versa), while friendliness or hostility is likely to elicit a warm or cold response, respectively (Kiesler 1983).

Rigid individuals may have more difficulty adapting their behaviour to fit a variety of social contexts, as their resistance to change may prevent them from considering the perspectives of others and responding appropriately to less familiar interactions (Kiesler 1983; Leary 1957; Tracey 2005). In line with increased threat sensitivity and neuroticism, it is possible that rigid individuals are more vigilant towards others who engage in interpersonal styles that do not complement their own. For example, dominant individuals who display a narrow range of social behaviours may feel threatened around other self-assured individuals and develop a more authoritarian approach to assert their views (e.g., Schultz et al. 1997), even if compliant or agreeable behaviour is more appropriate for the interaction. Future research is needed to determine the extent to which rigidity and sensitivity to threat contribute to lower quality of relationships and maladaptive attachment styles associated with the BAP (e.g., Jamil et al. 2017; Jobe and White 2007; Lamport and Turner 2014).

Comparison with Other BAP Studies on Emotion Recognition

Overall, our findings differ from those reported by Ingersoll (2010), who examined the association between emotion recognition across modalities and BAP features in the general population. Specifically, Ingersoll did not find a significant correlation between the recognition of angry prosody (or any other vocal emotion) and BAP features. Methodological differences could at least partially account for this discrepancy. Ingersoll (2010) used linguistic stimuli spoken in different emotional tones (e.g., "I'm going out of the room now and I'll be back later"), which could have been confounded due to possible interactions between the semantic and affective components in speech. Ingersoll also used the AQ to measure the BAP, whereas we used the BAPQ, which has better psychometric properties and a factor structure that corresponds well with the theoretical domains of the BAP (Ingersoll et al. 2011).

It is interesting to note that a correlation between higher self-ratings of BAP traits and poorer recognition of angry faces was found in Ingersoll's (2010) study. Other researchers have also reported a negative correlation between BAP traits and facial anger recognition in the general population, particularly for less intense expressions (Poljac et al. 2012). Our proposal of enhanced threat detection in the BAP may be specific to the auditory domain. This may reflect that anger cues in the voice are more arousing than anger cues in the face, and hence, serve as stronger signals of dominance or impending danger. Of note, research has shown that vocal affect bursts for anger are recognized more easily than their

facial equivalents (Hawk et al. 2009). The ability to detect angry voices may have a greater evolutionary advantage over angry faces, as it can alert the listener to the direction of an approaching threat even when the source of danger is out of view. Developmental studies have shown that infants can detect vocal emotions (and discriminate between positive and negative ones) earlier than facial emotions, likely due to earlier prenatal development of the auditory versus visual system (Caron et al. 1988; Fernald 1988; Walker-Andrews 1997). More research is needed to examine why individuals with higher levels of the BAP are sensitive to angry voices but not faces. Future studies using cross-modal paradigms to assess anger recognition in the BAP is also recommended.

Limitations

There are a number of limitations related to task design and the demographics of our sample. The MAV stimuli (Belin et al. 2008) were recorded by professional actors upon prompting and were therefore not elicited spontaneously. Some may therefore argue that our stimuli were only prototypes of emotional expressions, not portrayals of genuine affective states, which may affect the ecological validity of our study. For example, actor-portrayed stimuli may represent stronger affective states (e.g., higher intensity), as opposed to natural expressions of the same emotion. However, the use of actor portrayals has been a primary approach in emotion research because of the ethical considerations and practical difficulties associated with eliciting genuine emotional states in natural or controlled settings (Johnstone and Scherer 2000). Prototypes of emotional expressions are also appropriate for such studies because they often represent display rules, or social norms that dictate appropriate expression of emotions, which must be understood for effective communication (Scherer 2003). Further, our data showed a good distribution of intensity ratings across stimuli, suggesting variation in the strength of portrayed emotional states whereby not all stimuli were perceived to have high intensity.

On our computerized emotion recognition task, we did not control the number of times that participants were allowed to listen to each vocal stimulus, nor did we assess reaction time for correctly identified emotions. The latter may show greater sensitivity to individual differences in vocal emotion recognition. Despite these limitations, our accuracy rates were similar to those of Belin et al.'s (2008), indicating that our computerized task was reliable and robust for identifying differences in performance across the basic emotion categories. Further, our paradigm yielded positive correlations between recognition accuracy and intensity ratings across emotions, consistent with previous research on the role of emotion intensity in vocal emotion recognition (Juslin and Laukka 2001).

Our sample consisted of highly educated participants (the majority having completed, or currently completing, a postgraduate degree) whose mean IQ score fell in the High Average range. Therefore, our sample does not represent a wide distribution of intellectual functioning and educational background as expected in the general population. Despite this, our participants were from various cultural backgrounds, which may support the use of MAV stimuli in cross-cultural studies on auditory emotion processing. It is also worth noting that we did not find any significant gender differences across our emotion and BAP measures, suggesting that gender-related differences were unlikely to account for the anger-specific relationship with BAP features. A final point is that we did not formally assess mood symptoms (e.g., anxiety, depression). However, we asked participants to indicate whether they had a psychiatric history and accounted for any confounding effect of mental disorder on recognition accuracy by removing a participant (with comorbid depression and anxiety) from analysis since he was an outlier on the task.

Conclusion

In summary, this study provides new information about how BAP traits in the general population are related to vocal emotion recognition ability. We used a novel online paradigm to assess vocal recognition and intensity ratings for a selection of non-linguistic vocal affect bursts from the MAV battery. We found that the BAP dimension of rigidity was associated with enhanced recognition and higher intensity ratings specifically for angry voices. Our findings suggest that typically developing individuals with more rigid BAP traits are more sensitive to threatening stimuli within the auditory domain. Further research is warranted to understand the mechanisms underlying anger-specific associations in ASD and the BAP.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki

declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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7.8 Summary of Key Findings

- BAP traits in the general population do not impair the recognition of vocal affect bursts
- Higher levels of rigid BAP traits are associated with better recognition and higher emotional intensity ratings for angry voices
- This suggests heightened sensitivity to auditory threat signals in the BAP in the general population
- The anger-specific association with rigid BAP traits could be influenced by other personality factors, specifically neuroticism and trait anxiety, although further research is required to test this assumption
- Enhanced auditory threat detection in rigid individuals may have consequences for their interpersonal functioning

CHAPTER 8

General Discussion

8.1. Summary of Thesis Aims and Key Findings

1. This thesis examined the brain and behavioural correlates of emotional voice processing in ASD and the BAP, specifically for non-linguistic stimuli in the form of vocal affect bursts. As described in Chapter 1, two primary research questions were addressed:What is the profile of emotional voice processing abilities in ASD, the BAP in relatives, and the distribution of BAP traits in the general population?
2. What are the neurobiological substrates of emotional voice processing in individuals with ASD and relatives with the BAP?

Three studies were performed to address these research questions using the same purpose-built web-based task for measuring vocal affect burst recognition and/or fMRI task for eliciting brain activation. Implementing the same paradigms across studies allowed indirect inferences to be made about similarities and differences in the behavioural and neurobiological profiles of emotional voice processing between ASD and the BAP in the cohorts assessed here.

In response to the first research question, Study 1 (Chapter 5) revealed that individuals with ASD demonstrated a vocal emotion recognition deficit, by misclassifying neutral voices into basic emotion categories at a higher rate than controls. However, the ASD group classified vocal affect bursts of the six basic emotions into their respective categories as accurately as controls and also assigned similar intensity ratings to these stimuli. Study 2 (Chapter 6) revealed that relatives of individuals with ASD who met categorial criteria for the BAP on clinical assessment (i.e., BAP-positive status) showed intact vocal emotion recognition, classifying neutral and emotional voices into their respective categories at similar accuracy to controls. The BAP and control groups also assigned similar intensity ratings to the emotional stimuli. Study 3 (Chapter 7) revealed that higher self-ratings of BAP traits in the general

population correlated with higher recognition accuracy and emotional intensity ratings for angry vocal affect bursts. This relationship was specific to rigid BAP traits, suggesting that those with higher levels of rigidity had enhanced auditory threat detection. Therefore, different profiles of emotional voice processing abilities were observed in ASD and the BAP, ranging from a recognition *deficit* in individuals with ASD, *no deficit* in relatives with BAP-positive status, and *heightened sensitivity* to angry voices in individuals from the general population with higher levels of BAP traits (Figure 8.1).

Random and fixed-effects analyses (RFX and FFX) of whole-brain activation elicited by the fMRI task were used to address the second research question. Individuals with ASD (Study 1) and relatives with the BAP (Study 2) engaged similar task-relevant brain regions to their respective control groups to successfully classify vocal affect bursts. In both studies, FFX analyses alone (not RFX) revealed that activation was significantly higher in the ASD and BAP groups relative to controls (Figure 8.1). The atypical brain activation observed in the ASD and BAP groups can therefore only be inferred for the specific cohorts tested here, and cannot be generalised to the wider populations from which they were sampled. Specifically, the ASD group showed enhanced activation in widely distributed fronto-temporal, parietal, occipital, and cerebellar regions (associated with emotional voice processing, executive function, memory, and motor, somatosensory, and visual processing), whereas the BAP group showed a less extensive pattern of enhanced activation confined only to occipital regions. These FFX findings may be useful for informing new hypotheses about the role of neurobiological compensation for emotional voice processing in ASD and the BAP, including an exploration of potential endophenotypes of ASD. Such hypotheses should be assessed at the population level using larger samples which would enable more homogeneous subgroups within each cohort to be explored (see Sections 8.2.1 and 8.2.2 for further discussion).

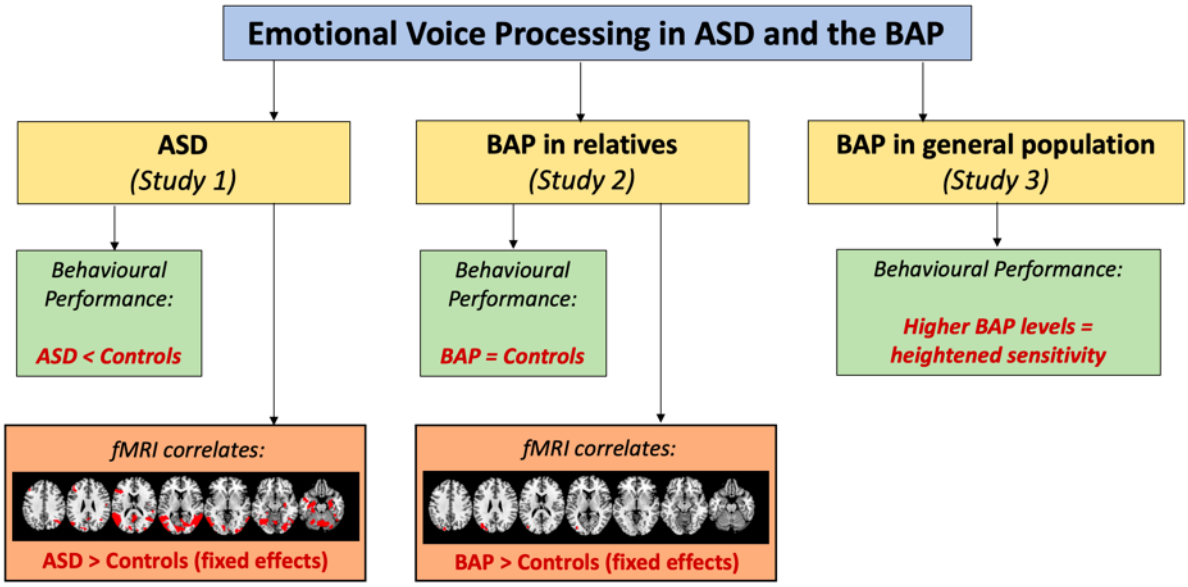


Figure 8.1. This figure summarises findings from Studies 1-3. It shows the profile of emotional voice processing abilities (i.e., performance on the web-based task) in ASD, the BAP in relatives, and the distribution of BAP traits in the general population. It also shows the profile of atypical, enhanced brain activation underlying emotional voice processing in the specific cohorts of individuals with ASD and relatives with the BAP assessed in this thesis under the fixed-effects model.

8.2. Implications of Findings and Directions for Future Research

Overall, this thesis makes important contributions to the literature on social cognition in ASD and the BAP. As reviewed in Chapter 3, our knowledge of social cognition in ASD and the BAP is primarily based on studies examining emotional face processing (e.g., inferring theory of mind or complex emotions from the eyes, empathising with others based on distress cues in their face, recognising and simulating basic facial emotions). Emotional voice processing in these populations has received much less attention, with existing studies largely focusing on the recognition of speech-embedded emotional prosody rather than non-linguistic expressions (Chapter 4). Here, vocal affect bursts were used across all three studies to eliminate the confounds of higher-order linguistic processing inherent in prosodic speech stimuli. Findings from the three studies therefore reflect relatively pure behavioural and neurobiological profiles

of emotional voice processing in ASD and the BAP, and have broader implications for research on the genetic aetiology of ASD.

8.2.1. Compensation for emotional voice processing in ASD

Livingston and Happé (2017) defined compensation as "the processes contributing to improved behavioural presentation of a neurodevelopmental disorder, despite persisting core deficit(s) at cognitive and/or neurobiological levels" (p. 731). Other terms used to describe this principle include "compensatory learning" or "adaptation" (Johnson, Jones, & Gliga, 2015; Lai et al., 2017; Livingston & Happé, 2017). Compensation allows individuals with a neurodevelopmental disorder to achieve a "good outcome" or normal levels of performance on behavioural testing by relying on additional cognitive resources that are not typically required by healthy controls (Livingston & Happé, 2017). Compensation may be inferred on a neurobiological level when individuals with the disorder demonstrate successful performance on behavioural tasks, but show atypical brain function (e.g., decreased/increased activation relative to controls) in task-relevant networks (Johnson et al., 2015; Livingston & Happé, 2017; Ullman & Pullman, 2015). Individuals with the disorder may also rely on alternate or additional brain networks to accomplish the same task (Johnson et al., 2015; Livingston & Happé, 2017; Ullman & Pullman, 2015).

Compensation may account for heterogeneity of the severity of social communication deficits among individuals with ASD. High-functioning individuals are typically better able to compensate for their underlying deficits (Livingston, Colvert, Bolton, & Happé, 2019; Livingston & Happé, 2017), consistent with research showing that higher IQ and verbal skills are strong predictors of progress in behavioural intervention programs, learning adaptive communication skills, and social competence (Ben-Itzchak & Zachor, 2007; Gillespie-Lynch

et al., 2012; Kenworthy, Case, Harms, Martin, & Wallace, 2010; Smith, Klorman, & Mruzek, 2015; Szatmari, Bryson, Boyle, Streiner, & Duku, 2003). Those with better executive function are also better able to compensate, likely through careful planning of appropriate social behaviour, inhibition of inappropriate social behaviour, and flexibility in coping with unpredictable changes during social interactions (Livingston & Happé, 2017). Further, individuals with ASD can rely on intact declarative memory to learn and retain knowledge about social conventions (Ullman & Pullman, 2015) as well as their systemising skills to develop rule-based strategies to compensate (Golan et al., 2010; Golan & Baron-Cohen, 2006; refer to Appendix B for a review on systemising).

Specific examples of compensation for social cognitive difficulties in ASD (Chapter 3) include the use of verbal mediation to reason about mental states on ToM tasks (e.g., "logical hacking", Happé, 1995; Scheeren, de Rosnay, Koot, & Begeer, 2013) or to achieve high performance on emotion labelling tasks (Grossman et al., 2000; Teunisse & de Gelder, 2001). For example, in Grossman et al.'s. (2000) study, participants were first shown an emotional face accompanied by either a matching or non-matching emotion label (e.g., happy face presented with the word "happy" or "afraid"), then required to identify the correct emotion in the face from a list of labels after a short delay. Individuals with ASD performed as well as controls on the matched condition, but more poorly than controls on the mismatched condition, often selecting the emotion indicated by the label instead of the face (e.g., "afraid" instead of "happy"). The authors reasoned that the ASD group relied on verbal strategies to perform the task, without necessarily having an intuitive understanding about emotions.

Individuals with ASD can rely on memory for social scripts or visual instructional cues (e.g., written prompts, pictorial cues) to direct their engagement with others (Ganz, Kaylor,

Bourgeois, & Hadden, 2008; Loveland & Tunali, 1991; Thiemann & Goldstein, 2001). They may also rely on feature-based rather than configural-based processing of the face to recognise specific emotions (Harms et al., 2010; Rutherford & McIntosh, 2007). In addition, ASD intervention programs that tap into an individual's systemising skills can facilitate emotion recognition (Golan et al., 2010; Golan & Baron-Cohen, 2006). For example, the "Transporters" DVD by Golan et al. (2010) teaches children with ASD how to recognise age-appropriate basic and complex emotions, using photos of human faces grafted on vehicles that move in a predictable manner (e.g., trains, cable cars, tractors). Studies have found that after 3-4 weeks, high-functioning children demonstrated improvement in emotion recognition ability, not just for faces included in the DVD, but also for unfamiliar faces which were not attached to vehicles (Golan et al., 2010; Young & Posselt, 2012). However, the intervention had limited benefits on children with low IQ, suggesting that they were less able to utilise systemising skills to facilitate emotion recognition (Williams, Gray, & Tonge, 2012).

Behavioural findings from the pre-scan task revealed that the ASD group was poorer than controls at classifying neutral voices. They confused neutral voices as being emotional, demonstrating a vocal emotion recognition deficit. However, when presented with emotional voices, they were able to classify them into their corresponding basic emotion categories as accurately as controls. The ASD group's intact classification of emotional voices may reflect the use of compensatory strategies, especially since all were high-functioning (mean IQ in the *High Average* range), suggesting that they at least had the intellectual capacity to compensate for underlying difficulties with social cognition. The ASD group's poorer recognition of neutral voices relative to controls may suggest that cognitive strategies did not facilitate the classification of neutral voices in the ASD group to the same extent as emotional ones due to their ambiguity. In contrast to emotional voices, the significance (or lack thereof) of neutral

voices is unlikely to be reinforced through intervention programs or everyday interactions with others. Accordingly, perhaps the participants with ASD were unlikely to apply learnt strategies to distinguish the absence or presence of emotions in monotonous, neutral voices that do not serve a clear purpose for social communication in everyday life.

The assumption that the ASD group used compensatory strategies to classify basic emotions is reasonable when considered with their enhanced brain activation relative to controls based on FFX analyses of the fMRI data. Specifically, the FFX analyses revealed significantly higher activation in the ASD group relative to controls across regions implicated in emotional voice processing, memory, executive function, and visual/face processing (among others), despite both groups performing at ceiling levels on the fMRI task. Accordingly, members of the ASD group could have possibly engaged more cognitive resources to achieve a similar performance to controls on behavioural measures, as summarised in Table 8.1. Of note, supplementary analyses also showed that higher activation in the bilateral IFG (associated with the cognitive evaluation of emotional voices) correlated with more severe symptoms (i.e., based on informant-ratings on the SRS-2) in the ASD group.

Table 8.1

Potential Compensatory Strategies for Vocal Emotion Recognition That Correspond to Enhanced Brain Activation in the ASD group Relative to Controls Under FFX Analyses (Study 1)

Regions with Enhanced Activation and Their Associated Functions	Potential Compensatory Strategies
Emotional voice processing: Left IFG, STS/MTG; bilateral STG and MTG	• Increased auditory selective attention to extract/integrate acoustic cues from the voice and to make judgments about their emotional content • Greater reliance on feature-based processing of acoustic cues in the voice
Cognitive control and semantic processing: Left MFG, IFG, middle temporal pole; cerebellum	• Increased semantic processing, working memory, response selection, inhibition, conflict monitoring for classifying emotional voices • Covert verbal mediation (e.g., inner speech) to reason about emotional voices or match them to emotion labels
Visual processing: Bilateral calcarine sulci, lingual gyri, cuneus, lateral occipital gyri (superior, middle, inferior), fusiform gyri	• Increased cross-modal representation, like imagining visual cues/faces associated with the emotional voice • Increased auditory attention[a]
Memory: Bilateral hippocampi, precuneus; left parahippocampal gyrus, angular gyrus; right amygdala (specific to emotional memories)	• Retrieval of episodic memories, including those with an emotional and autobiographical context

Note. IFG = inferior frontal gyrus; STS = superior temporal sulcus; STG = superior temporal gyrus; MTG = middle temporal gyrus; MFG = middle frontal gyrus.

[a]Enhanced activation in the visual network could have resulted from attention-related modulations in temporal voice areas (e.g., STS/MTG/STG) through temporo-occipital connections (Cate et al., 2009; Ethofer et al., 2012).

It is important to note, however, that inferences about group differences based on FFX analyses cannot be extended to the ASD population as a whole, since no significant group differences were detected using RFX analyses. Only a trend towards enhanced activation (in a subset of regions similar to those indicated by the FFX analyses) in ASD was observed at an uncorrected significance threshold under the RFX model. Interestingly, fMRI studies assessing emotional voice processing for speech prosody have also reported a trend (at uncorrected thresholds under the RFX model) for enhanced brain activation in ASD within regions serving cognitive control, attention, social cognition, and memory (Eigsti et al., 2012; Gebauer et al., 2014).

RFX analyses are less sensitive to group differences than FFX analyses, since they have lower statistical power (which corresponds to the sample size, not the total EPI volumes across participants) and account for between-subject variance (K. J. Friston et al., 1999; Penny & Holmes, 2003). Heterogeneity is a hallmark of ASD, with vast differences in aetiology (e.g., genetic variation, environmental risk factors), early brain development, comorbidities (e.g., psychiatric/medical), clinical presentation, cognitive function, and outcome expected among individuals who share the same diagnosis (Lenroot & Yeung, 2013; Livingston & Happé, 2017; Masi, DeMayo, Glozier, & Guastella, 2017). Accordingly, these sources of heterogeneity are likely to contribute to high between-subject variance of brain activation on fMRI paradigms, which may hinder the detection of group differences based on RFX analyses. Under the FFX model here, it is possible that only subgroups of participants within the ASD cohort (rather than all 16 participants, per se) showed strong activation in the regions implicated in the direct comparison between groups. Therefore, a systematic exploration of hypotheses related to neurobiological compensation in ASD at a population level would require sample sizes that are large enough to enable the assessment of more homogenous subgroups.

In addition to the potential sources of heterogeneity listed above, between-subject variability in this specific ASD cohort may have been influenced by the use of different cognitive strategies (e.g., pathways for compensation) to classify basic emotions in vocal affect bursts. Future studies may therefore incorporate additional behavioural measures to account for how each participant approached the task. For example, post-hoc interviews and thematic analyses would be useful for identifying the range of key cognitive strategies used by ASD participants to classify emotional voices on the fMRI task, and to group participants accordingly. Alternatively, self-report measures may allow participants to rate how often they used specific cognitive strategies from a pre-defined list, such as those from Table 8.1 (e.g., "When performing the task, I paid close attention to the acoustic features of the voice/imagined emotional faces that accompany the voice/remembered specific events where myself or others expressed emotion; rate from *0 = did not apply to me at all* to *5 = applied to me on most trials*). A dimensional measure like this would also allow researchers to examine brain-behaviour correlations between the extent of reliance on a specific cognitive strategy and the strength of activation in corresponding regions.

Future studies could also examine the recognition of vocal affect bursts and its neural correlates in low-functioning individuals or younger children with ASD, who may be less capable of compensating for their social cognitive deficits. Identifying similarities and differences in brain activation between low- and high-functioning samples may allow researchers to disentangle atypical brain function related to compensatory strategies versus a deficit in emotional voice processing per se. It is recommended that future fMRI studies with a verbal component (e.g., forced-choice discrimination paradigms like the one used here) account for poor verbal abilities in low-functioning individuals by first ascertaining that they can read and comprehend what each emotional word label means. The present task design can be modified

to ensure that low-functioning individuals find the fMRI task achievable, such as allowing a longer time for participants to select their responses (e.g., > 2 s) or administering more practice trials. Alternatively, participants may be asked to make simpler "yes/no" judgments to verbal prompts presented aurally (e.g., "Is this an angry voice? *[Play sound]*"). Importantly, low-functioning individuals should be compared to an age- and IQ-matched control group (e.g., other neurodevelopmental conditions like Down Syndrome) to ensure that any group differences in behavioural performance or brain activation are not confounded by the effects of low intellectual functioning.

It would also be interesting to examine the effects of social skills training on neurobiological compensation for emotional voice processing in ASD. This may possibly be achieved by comparing patterns of brain activation before and after the implementation of specific interventions that have been shown to improve vocal emotion recognition abilities in ASD. One such intervention may be the "Mind Reading" computer program (Baron-Cohen, Golan, Wheelwright, & Hill, 2004),which has been shown to improve high-functioning children's emotion recognition abilities for both facial and vocal expressions (speech prosody) after 12 weeks, with gains maintained at follow-up five weeks later (Thomeer et al., 2015). This intervention consists of structured lessons and in vivo rehearsal (one-on-one with an examiner) for teaching children to define facial and vocal expressions of emotion, as well as games, quizzes, and rewards to reinforce their learning. It incorporates strategies for directing attention towards core emotional features of the face and voice, rule-based learning (e.g., systemising), and repeated practice to facilitate the improvement of emotion recognition skills. These strategies may ultimately be reflected in atypical brain activation post-intervention, despite improvements to emotional voice processing abilities on behavioural testing.

8.2.2. Endophenotypes of emotional voice processing in ASD

In Study 2, ASD-relatives were directly compared to controls (i.e., a different group from those assessed in Study 1) to determine the brain and behavioural correlates of emotional voice processing in the BAP. The BAP group demonstrated intact vocal emotion recognition on the pre-scan task, classifying both neutral and emotional voices into their respective categories as accurately as controls. Like the direct group comparisons in Study 1, only FFX (but not RFX) analyses revealed significant differences in brain activation between the BAP and control groups, although RFX analyses revealed a trend (at an uncorrected significance threshold) towards higher activation in the BAP group in left occipital regions and the left fusiform gyrus. Specifically, the FFX analyses revealed that the BAP group had significantly higher brain activation in the left lateral occipital cortex compared to controls, although both groups classified vocal affect bursts at ceiling levels on the fMRI task. Importantly, these findings only indicate atypical brain activation specific to the cohort of ASD-relatives tested here, which cannot be generalised to the wider population of ASD-relatives with the BAP.

As per Study 1, it is possible that group differences did not emerge under the RFX model due to its relatively low statistical power, and possibly, also due to high between-subject variability in the BAP group. There are some identifiable sources of heterogeneity in the BAP group. For example, participants comprised a mix of parents, siblings, and second-degree relatives from different multiplex families, which could indicate heterogeneity in the relative recurrence risk of ASD and a range of genetic/environmental risk factors (Sandin et al., 2014). Most participants also had multiple behavioural markers of the BAP (i.e., being socially unaware, pedantic, aloof, and/or obsessive), as determined on routine clinical assessment of all relatives enrolled in the Collaborative Autism Study .

Accordingly, the FFX effects could have been driven by a potential subgroup of participants within the BAP cohort (rather than all 13 participants per se) who showed strong activation in the left lateral occipital cortex. It is therefore recommended that future fMRI studies on emotional voice processing in the BAP include larger samples that would enable the exploration of more homogenous subgroups of ASD-relatives (e.g., parents-only, siblings-only, aloof-only, pedantic-only), who may have distinct neurobiological profiles. A larger sample size could also enable the exploration of potential subgroups who used different cognitive approaches to recognise vocal affect bursts, given that behavioural measures are also included to account for these forms of individual differences, as recommended for Study 1 (Section 8.2.1).

Despite the limited inferences that can be drawn from the FFX findings, the atypical brain activation observed in the BAP group may still be valuable for informing hypotheses about neurobiological endophenotypes of emotional voice processing in ASD. As described in Section 2.4.2, endophenotypes are intermediate phenotypes of a diagnostic state (Almasy & Blangero, 2001; Flint & Munafò, 2007; Gottesman & Gould, 2003). They are heritable, state-independent, co-segregate with the disorder in families, and occur at higher rates in relatives of individuals with the disorder than in the general population (Gottesman & Gould, 2003). The identification of endophenotypes may facilitate gene discovery for ASD, since they are likely to be associated with fewer genes and biological pathways than the disorder itself (Almasy & Blangero, 2001; Gottesman & Gould, 2003).

Neurobiological endophenotypes are particularly informative for research investigating the genetic aetiology of ASD, since they reflect genetic liability for the disorder even in the absence of observable deficits on behavioural testing (Hariri & Weinberger, 2003; Meyer-Lindenberg

& Weinberger, 2006). In Study 2, the enhanced activation in the left lateral occipital cortex was not unique to the BAP group, but was also observed in the ASD group (relative to their respective controls), who demonstrated enhanced activation across more extensive regions under the FFX model in Study 1. These findings may hint at the potential for a similar, but milder, expression of neurobiological compensation for emotional voice processing in the BAP compared to ASD, which would also suggest that the former has more subtle underlying emotional voice processing difficulties to compensate for (Figure 8.2). This hypothesis should be investigated at the population level using more robust methods. For example, the ASD and BAP groups were not directly compared in this thesis due to the large age disparity between the groups, as most ASD participants were in their teens to early 20s, whereas most BAP participants were in their 40s to 50s. Future studies examining neurobiological endophenotypes should therefore include larger, more homogenous samples of ASD and BAP participants (plus a control group) who are sufficiently matched on age to allow the direct comparison of brain activation and behavioural performance between groups.

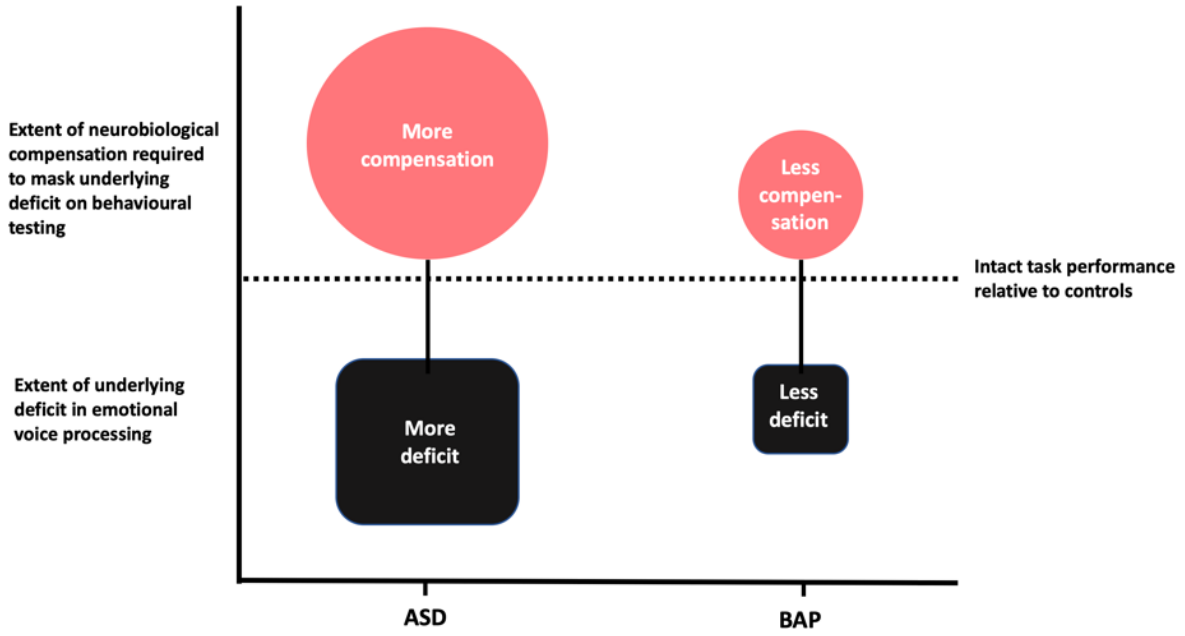


Figure 8.2. The relative degree of neurobiological compensation hypothesised to mask subtle, underlying emotional voice processing deficits on behavioural testing in individuals with ASD and the BAP, so that they are able to achieve a similar level of task performance to controls.

8.2.3. Auditory threat detection and BAP traits in the general population

Study 3 revealed an interesting, but unexpected, finding of a relationship between increased sensitivity (classification accuracy and intensity ratings) to angry voices and higher levels of rigid BAP traits in the general population of individuals without a family history of ASD. This indicates that BAP features may not impair emotional voice processing in the general population, but instead, in some instances, may serve an advantage. No associations were found between other BAP features (i.e., aloofness, pragmatic language difficulties) and recognition accuracy or intensity ratings for affect bursts representing other basic emotions. It is surprising that rigidity alone correlated with vocal emotion recognition, given that it can be considered a "non-social" component of the BAP (Sasson, Nowlin, et al., 2013). There are some social consequences for rigidity, however, as individuals who are more rigid are less likely to be flexible in social situations, and can have difficulty adapting to the interpersonal styles of others (e.g., Kiesler, 1983; Tracey, 2005; see Section 7.5.3)

The anger-specific association with BAP traits in the general population suggests that individuals who are more rigid have a heightened ability to detect threatening signals within the auditory domain. This effect was not observed for voices signalling fear, however, suggesting that it was specific to approach-related rather than avoidance-related threat signals (Bossuyt, Moors, & De Houwer, 2014; Carver & Harmon-Jones, 2009). Sensitivity to angry expressions has an evolutionary significance, as it allows individuals to respond quickly to approaching danger. This is exemplified in the "anger superiority effect", a phenomenon in which individuals are more sensitive to angry faces compared to friendly or non-threatening ones (Hansen & Hansen, 1988; Öhman, Lundqvist, & Esteves, 2001). The anger superiority effect is also demonstrated by individuals with ASD (Ashwin, Wheelwright, & Baron-Cohen,

2006; Isomura, Ogawa, Yamada, & Shibasaki, 2014; Rosset et al., 2011), although it is unclear whether rigidity per se contributes to this finding.

Further research is required to uncover the mechanisms underlying the relationship between higher levels of rigid BAP traits and increased sensitivity to angry voices. Study 3 proposed that underlying personality factors like neuroticism and high trait anxiety may account for this relationship (Section 7.5.3). This assumption is drawn primarily from research showing that neuroticism and high trait anxiety are not only associated with higher levels of BAP traits (Austin, 2005; Wainer et al., 2011; Wakabayashi, Baron-Cohen, & Wheelwright, 2006), but also with attentional bias to unpleasant emotional information and a tendency to appraise everyday situations or ambiguous stimuli as being negative (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzenboorn, 2007; Gomez, Gomez, & Cooper, 2002; Lommen, Engelhard, & van den Hout, 2010; Watson & Clark, 1984). Future studies should test the role of neuroticism and/or trait anxiety for mediating the rigid-anger effect along the lines of the model proposed in Figure 8.3. Future studies could also explore the extent to which the rigid-anger relationship influences one's ability to engage in complementary, pro-social behaviour (Section 7.5.3).

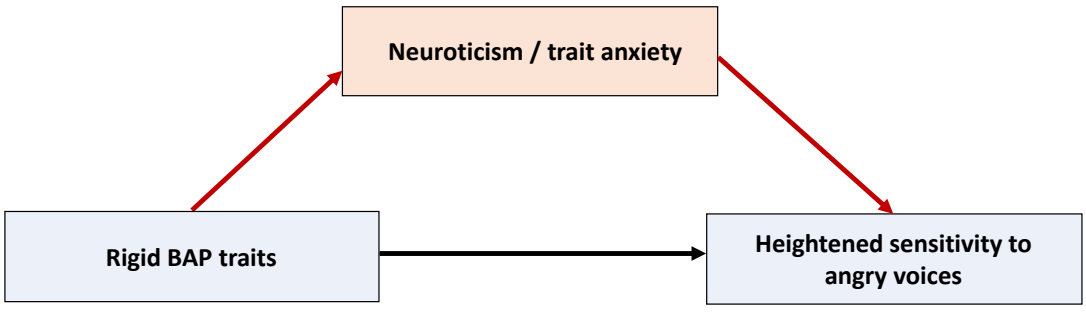


Figure 8.3. Proposed model of the relationship between rigid BAP traits, neuroticism/trait anxiety, and heightened sensitivity to angry voices. Here, it is hypothesised that rigid BAP traits influence heightened sensitivity to angry voices through an indirect pathway (red arrows) mediated by neuroticism/trait anxiety.

Enhanced auditory threat detection has not been reported in individuals with ASD and ASD-relatives, as previous studies have shown the opposite pattern, where these groups demonstrate poorer recognition of angry voices compared to controls (Oerlemans et al., 2014; Philip et al., 2010; Vannetzel et al., 2011). Similarly, the ASD and BAP groups from Studies 1 and 2 demonstrated lower recognition accuracy and intensity ratings for angry voices compared to controls (see Figures 5.5 and 6.2), although group differences did not reach statistical significance. It is therefore possible that different genetic processes account for enhanced auditory threat detection in the BAP in the general population, relative to individuals with ASD and family members with the BAP. In a similar vein, the overarching differences in profiles of emotional voice processing abilities between ASD, the BAP in relatives, and the distribution of BAP traits in the general population (Figure 8.1) suggest that gene-brain-behaviour interactions may differ across groups. These assumptions are only speculative, however, and warrant further investigation.

Neuroimaging measures can be employed to better understand the relationship between enhanced auditory threat detection and BAP traits in the general population. It would be particularly interesting to examine whether activation in the amygdala to threatening stimuli is moderated by rigid BAP traits and neuroticism or trait anxiety in the general population. Of note, fMRI research on face processing has reported an association between amygdala activation and threat perception in ASD (Kleinhans et al., 2010; Tottenham et al., 2014; see also Section 3.4.3). Among individuals with ASD, those with more severe social anxiety show higher amygdala activation when processing emotional faces depicting anger and fear (Kleinhans et al., 2010). Higher amygdala activation in ASD also correlates with higher threat ratings to neutral faces under conditions where gaze is manipulated towards the eye region (Tottenham et al., 2014).

8.3. General Limitations

8.3.1. Task design

There were a number of methodological limitations shared across studies (see also the "Limitations" section of Chapters 5-7). The vocal affect bursts employed in the behavioural and fMRI tasks were not elicited spontaneously but portrayed by professional actors (MAV; Belin et al., 2008). Actor portrayals of emotional expressions are typically exaggerated for recognisability, whereas expressions that occur spontaneously are more subtle (Scherer, 2003). It is possible that individuals with ASD will have difficulty compensating for the recognition of less prototypical expressions, which are more representative of the dynamic range of expressions one encounters in everyday social interactions. Of note, however, the use of actor portrayals is the most common approach for emotion research in clinical and non-clinical populations. Actor portrayals are appropriate for the context of this thesis, since they reflect social norms for the expression of emotions (e.g., "display rules") that must be accurately discerned for effective social communication. Further, their high recognisability on the fMRI task suggests that they were appropriate for yielding brain activation related to the processes of interest (e.g., vocal emotion recognition) rather than the confounds of task difficulty.

On each trial of the web-based task, participants were permitted to replay each MAV stimulus as often as needed before selecting a response. However, no data were collected to indicate the number of times the MAV stimuli were replayed. Further, reaction time on this task was not measured. On hindsight, it would have been beneficial to assess whether the ASD and BAP groups required more exposure to the stimuli (e.g., more replays), and whether they were slower at responding than controls, lending further support to the use of compensatory mechanisms for accurate task performance. These measures may be more sensitivie to subtle

emotional voice processing deficits in ASD and the BAP. For example, some studies on the recognition of emotional speech prosody have reported that individuals with ASD show similar accuracy rates, but slower reaction time, compared to controls (Ketelaars et al., 2016; Matsumoto et al., 2016). Further, all groups of participants (including controls) across Studies 1 to 3 had an almost perfect score for the classification of MAV stimuli representing happiness, which were all prototypes of laughter. Future studies may account for a wider variation of scores and increase task difficulty including stimuli that represent more subtle expresssions of happiness (e.g., sighs of pleasure).

The fMRI task was modelled as a block design, where "emotion blocks" alternated with "baseline blocks". Brain activation related to emotional voice processing was determined by contrasting the activation on the two blocks (e.g., "emotion > baseline" T-contrast). On each emotion block, participants were presented with a mix of vocal affect bursts representing all six basic emotions. As such, brain activation reflected neurobiological substrates for the recognition of vocal affect bursts in general, rather than specific emotions. We were therefore unable to infer emotion-specific activity (e.g., for angry voices alone) in the ASD, BAP, and controls groups. Of note, some studies have reported distinct patterns of brain activation for the perception of specific emotions in the general population (e.g., Phan, Wager, Taylor, & Liberzon, 2002), which will be interesting to interrogate in ASD and the BAP.

Future studies assessing the recognition of vocal affect bursts in ASD and the BAP may also include additional measures to determine levels of alexithymia across participants, which were not accounted for in this thesis. There is a growing body of evidence indicating that both facial and vocal emotion recognition abilities correlate positively with self-reported levels of alexithymia (Bird & Cook, 2013; Cook et al., 2013; Grynberg et al., 2012; Heaton et al., 2012;

Kätsyri et al., 2008; Ketelaars et al., 2016). This suggests that levels of alexithymia may also account for heterogeneity of behavioural performance and corresponding brain activation among individuals with ASD and the BAP. Measures assessing one's awareness or understanding of their own emotions may therefore allow researchers to disentangle the effects of alexithymia from ASD symptomatology or BAP traits on vocal emotion recognition abilities.

8.3.2. Sample selection

In Studies 1 and 2, the sample sizes of the ASD (n = 16), BAP (n = 13), and control groups (n =16 and n = 13) were small, due to the limited budget for MRI scanning. The small sample size may have contributed to low power for detecting group differences in behavioural performance on the pre-scan task (e.g., for ASD vs. controls on emotional trials in Study 1; for BAP vs. controls on emotional and neutral trials in Study 2) and group differences in brain activation under RFX analyses. As already discussed, there were also several potential sources of heterogeneity within the ASD and BAP groups, which could have contributed to high between-subject variability in brain activation. For example, 50% of participants with ASD (n = 8) had a mix of psychiatric comorbidities (e.g., ADHD, anxiety, and/or depression), for which they received a wide range of pharmacological treatments. The BAP group comprised a mix of different types of first- and second-degree relatives (e.g., parents, siblings, grandparent, first-cousin), and most had multiple behavioural markers of the BAP as determined on routine clinical assessment by the CATS team (e.g., socially unaware, pedantic, aloof, and/or obsessive). Further, the ASD and BAP groups were not age-matched and were therefore, not directly compared on behavioural and neuroimaging measures.

Study 1 was conducted exclusively on high-functioning individuals with ASD who had mean Full-Scale, Verbal, and Performance IQ in the *High Average* range. Therefore, the behavioural

and neuroimaging findings from Study 1 may not be generalisable to individuals with comorbid ASD and intellectual disability. As discussed in Section 8.2.1, individuals with lower intellectual function are likely to demonstrate poorer performance than individuals with ASD and controls on behavioural measures of emotional voice processing, possibly because they are less able to acquire and apply strategies to compensate for their deficits. In addition, the individuals from Study 1 were primarily male (only three females in a total sample of 16 participants). Future studies should include a more even sample of male and female participants to determine sex-specific effects on the brain and behavioural correlates of emotional voice processing in ASD. Of note, studies have reported sex differences for social cognition (among other functions like systemising) and social brain function in individuals with ASD (Auyeung et al., 2009; Baron-Cohen & Wheelwright, 2004; Hall et al., 2012; Hull, Mandy, & Petrides, 2017).

In Study 3, emotional voice processing abilities were correlated with the *continuous distribution* of BAP traits in the general population. Participants were not divided into BAP-positive and BAP-negative groups according to categorical criteria (e.g., BAPQ cut-off scores). Future studies can compare emotional voice processing abilities between equal numbers of participants from the general population with and without BAP-positive status, to provide further insight into components of the BAP in individuals without a family history of ASD.

8.4. Conclusions

This thesis explored emotional voice processing and its neurobiological substrates in ASD and the BAP, using vocal stimuli that consisted of basic non-linguistic emotional expressions (vocal affect bursts). Behavioural findings indicated that deficits in vocal emotion recognition (i.e., misclassification of neutral voices as expressing basic emotions) were unique to

individuals with ASD and did not extend to ASD-relatives with BAP-positive status or to individuals from the general population with higher levels of BAP traits. In contrast, higher levels of rigid BAP traits in the general population were associated with enhanced auditory threat detection. Neuroimaging findings based on random-effects analyses indicated that brain activation in the ASD and BAP groups did not differ from controls, presenting no evidence for atypical brain activation in the wider ASD and BAP populations. However, fixed-effects analyses revealed that the two groups showed enhanced brain activation relative to controls on a sample level, which may have implications for future studies investigating neurobiological compensation in ASD and the BAP, as well as potential endophenotypic markers in ASD. Overall, this thesis provides important insights into social cognition in ASD as it relates to emotional perception in voices in ASD and the BAP, and may provide useful information for future researchers investigating genetic factors and biological networks contributing to social communication deficits in ASD.

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APPENDICES

APPENDIX A

"Emotions and Me"

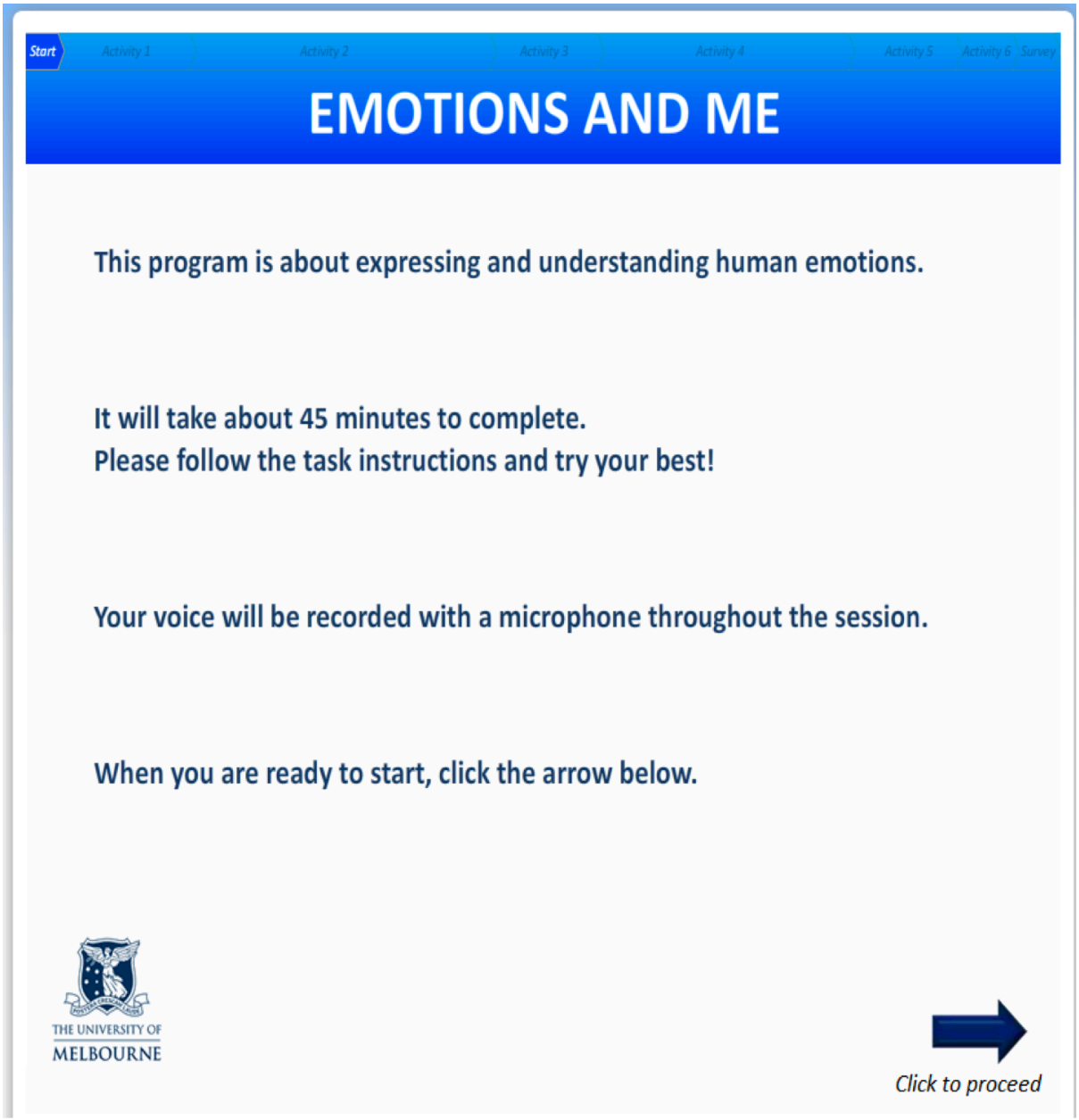
This appendix shows the interface of a web-based program designed by the PhD candidate and colleagues (during the course of candidature) entitled "Emotions and Me" (Yap, Solly, McLachlan, & Wilson, 2013)[1]. This program was designed to assess the expression, recognition, and imitation of non-linguistic emotional vocalisations (vocal affect bursts) across clinical and non-clinical populations. It assesses vocal affect bursts for the six basic emotions (i.e., anger, disgust, fear, happiness, sadness, and surprise) and a neutral category. This program also assesses pitch processing and includes a short questionnaire about the participant's musical abilities. These additional, supplementary tasks may be used to make further inferences about the participant's performance on emotion-related tasks (e.g., determining whether poor imitation of vocal emotions simply reflects poor perception of pitch). Of note, the emotion recognition task alone was employed for Studies 1-3 (Chapters 5-7).

The following screenshots show the different tasks in the order they appear in the program:

[1] Citation: Yap, V. M. Z., Solly, M., McLachlan, N. M., & Wilson, S. J. (2013). Emotions and Me. Unpublished instrument. Retrieved from http://emotions.sollysweb.com/index_new.php

I. Introduction

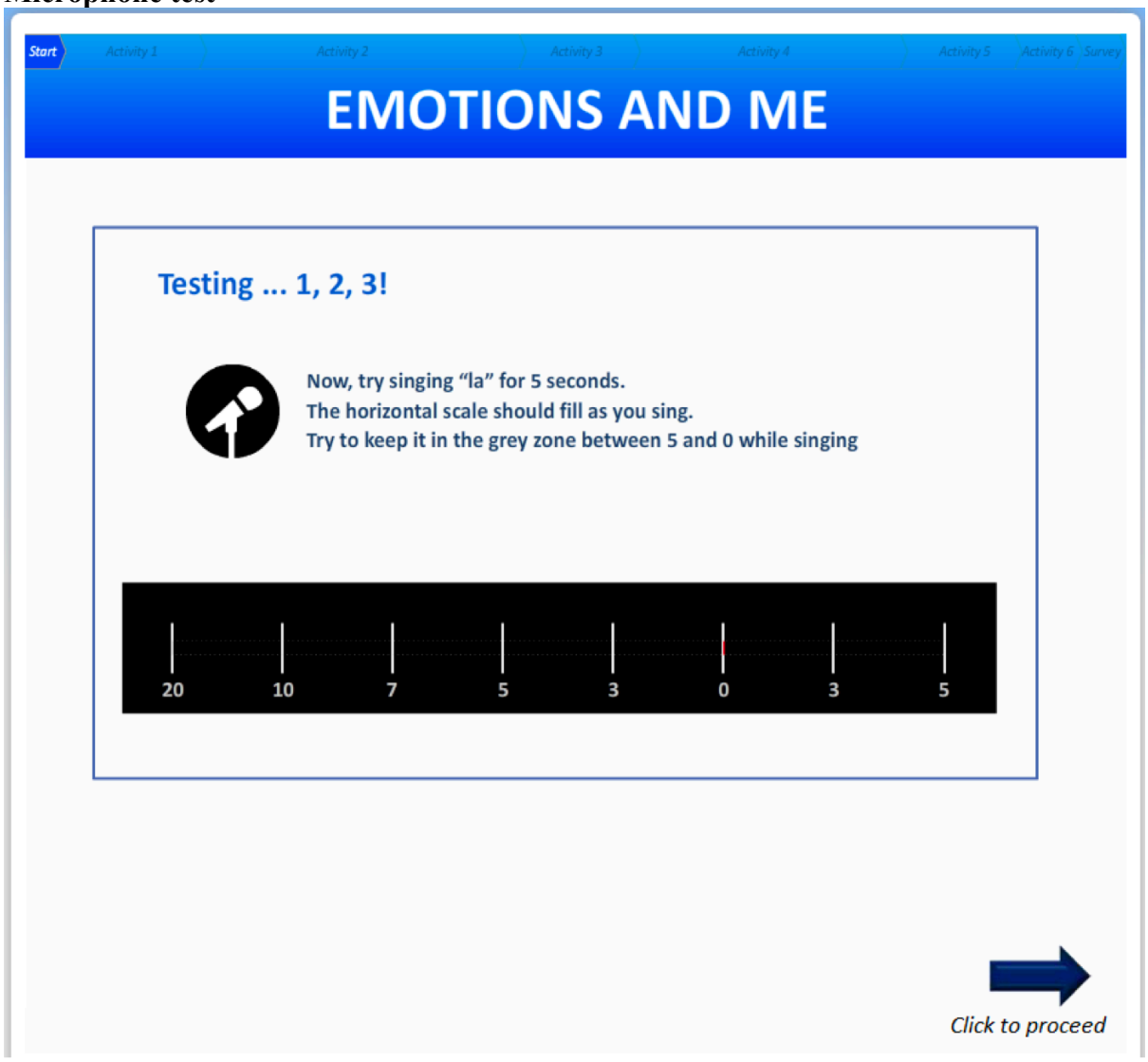
Overview of program



Participant information

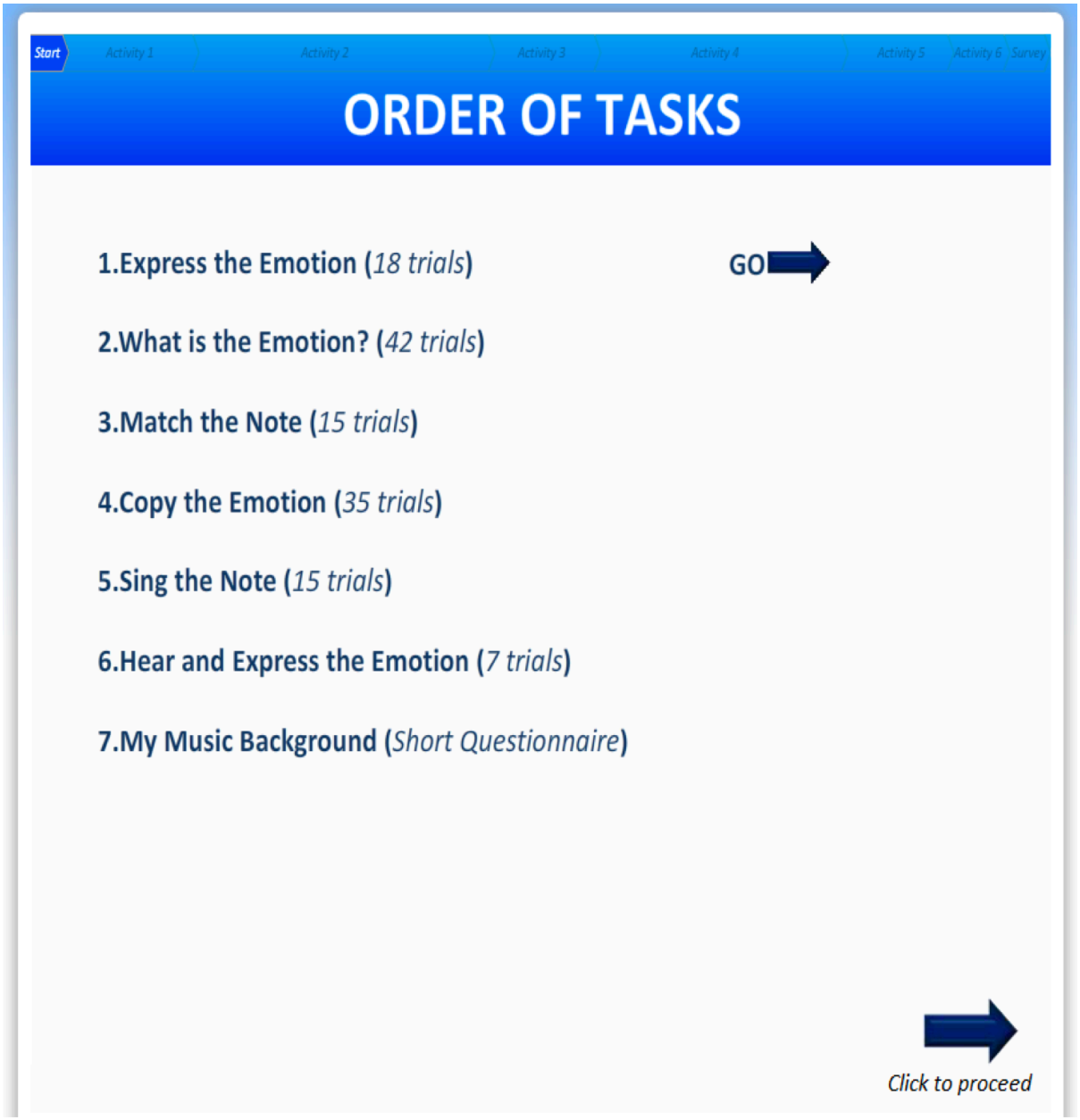


Microphone test



**It is recommended that participants complete this program in a quiet space. While an in-built computer microphone is sufficient for data collection, we used professional audio recording equipment (Zoom H4n) to ensure the optimum quality of voice recordings for all participants.*
**The black bar here (and in various tasks) serves as a sound meter to indicate the volume of the participant's voice.*

Task selection

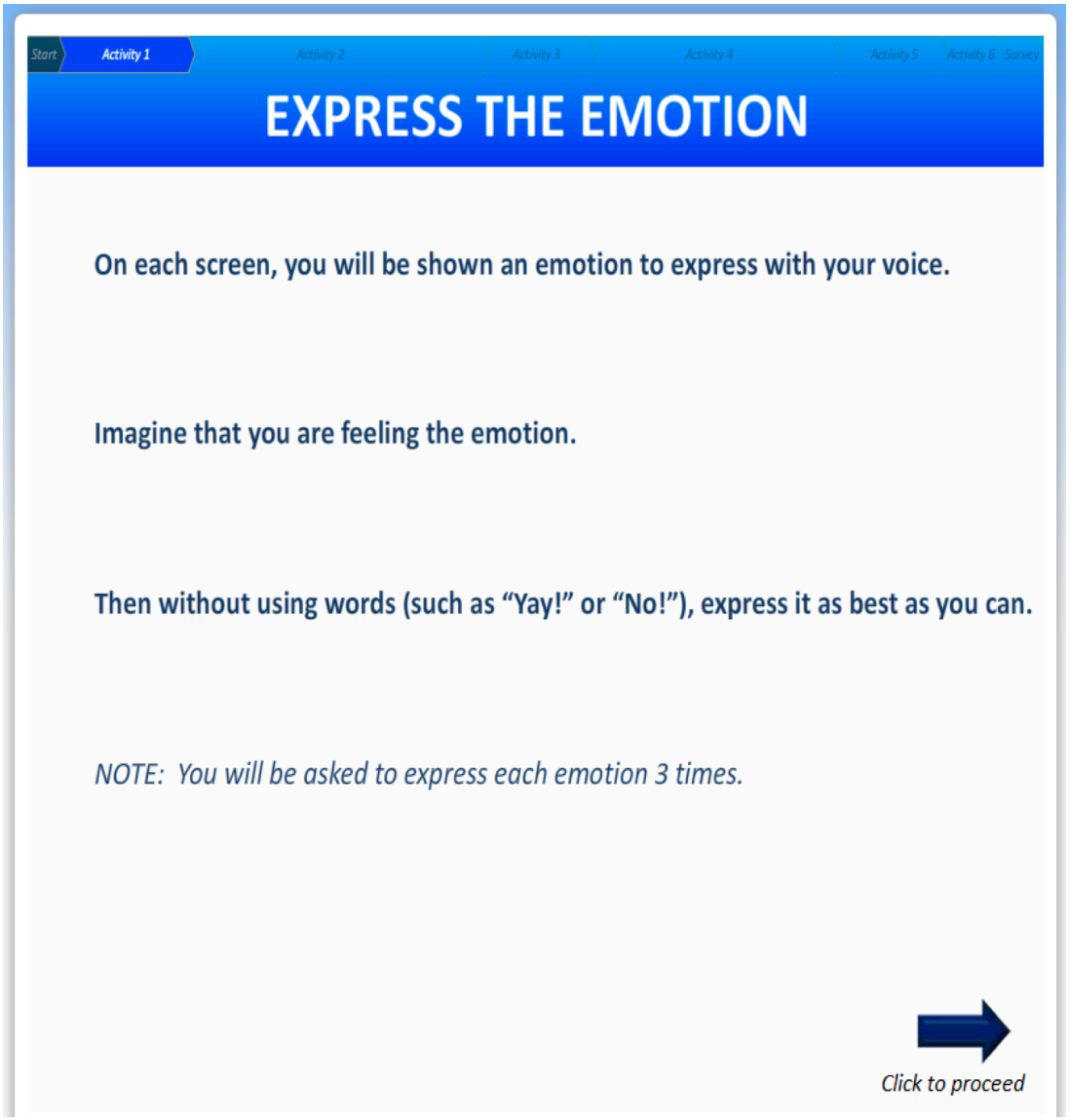


**Specific tasks can be selected here; otherwise the program begins with the first task by default.*

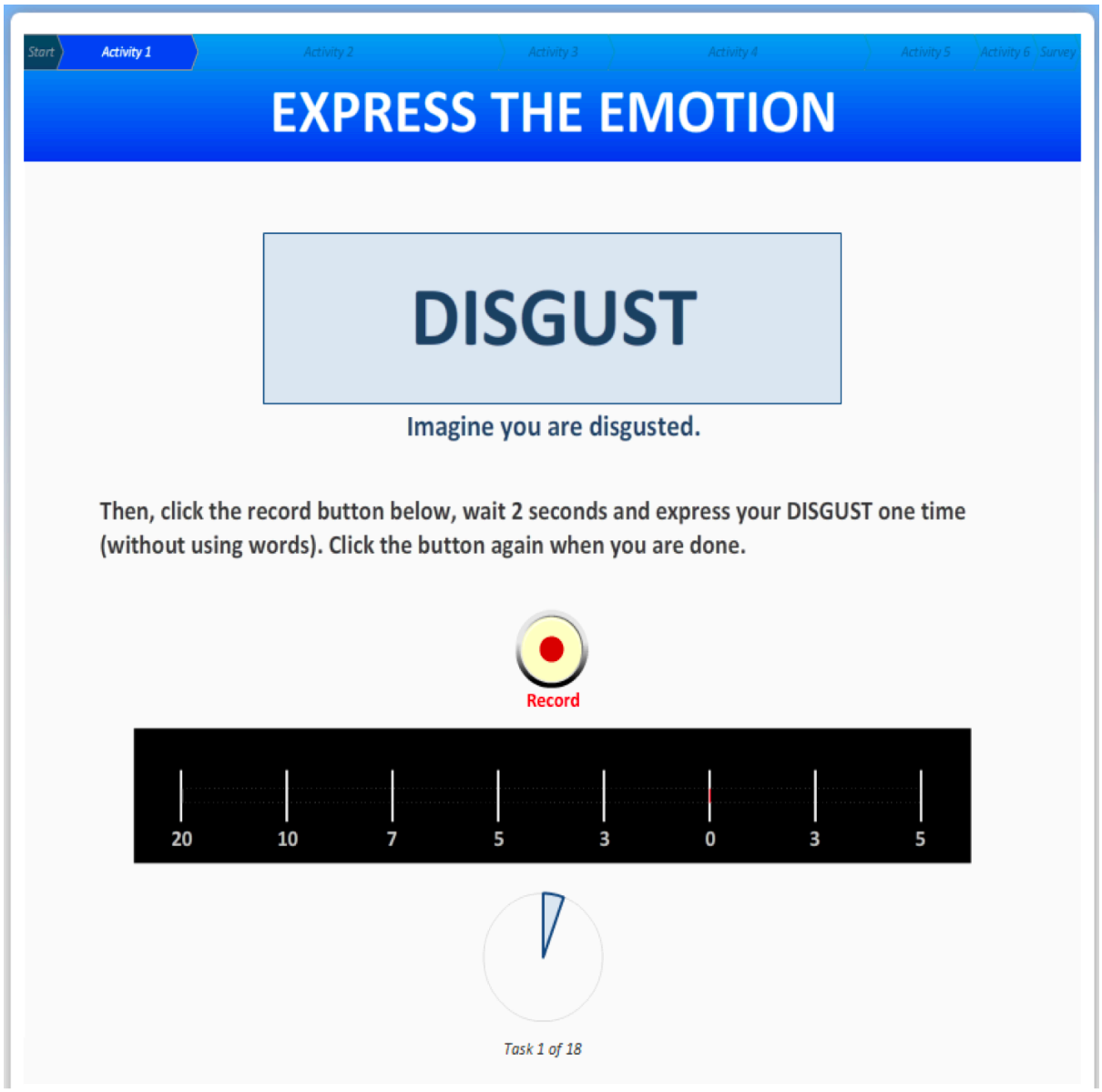
II. Emotion Expression

Participants are required to imagine that they are feeling a specific emotion, then to express it vocally without using words. Participants are instructed to express each emotion three times across three consecutive trials (6 emotions x 3 trials = 18 total trials). The order of basic emotions is randomised across participants.

Task overview



Trial 1 of 3 for "Disgust":

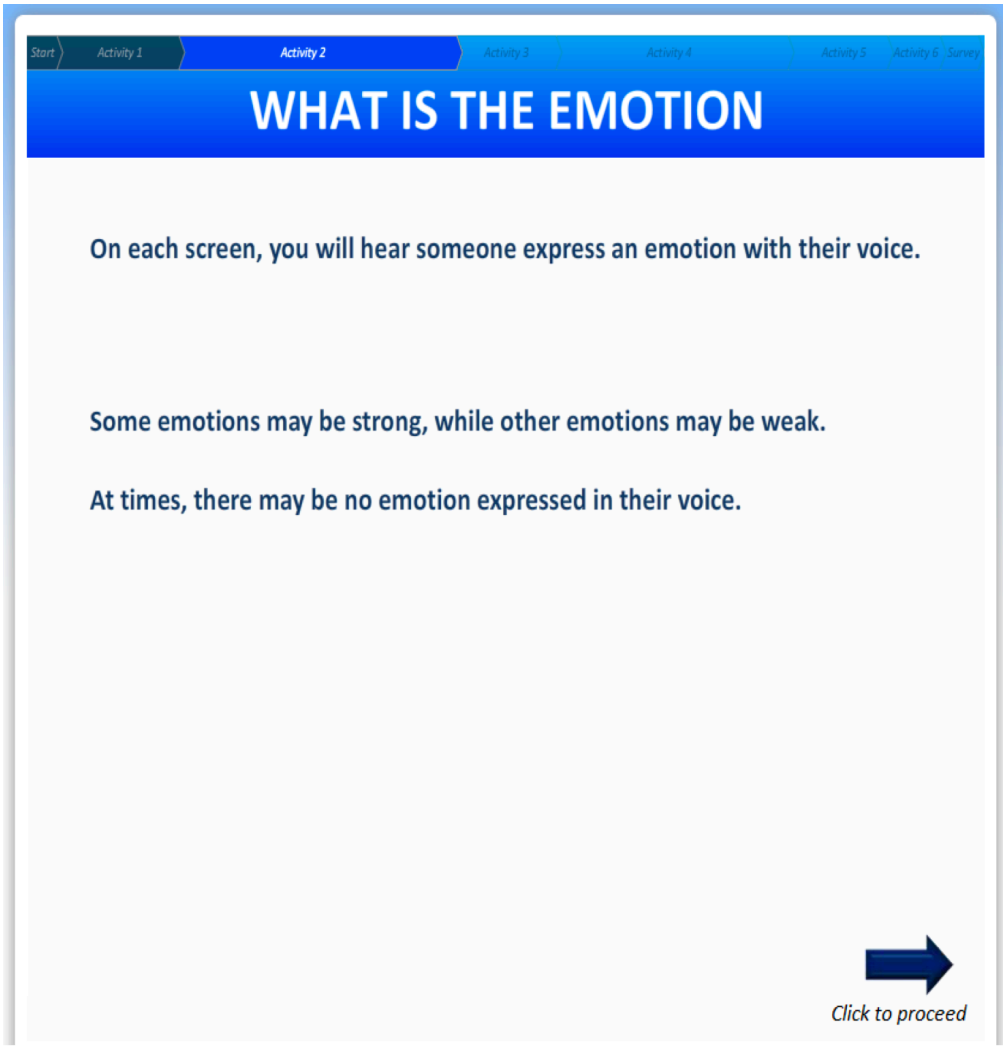


**The interface for Trials 2 and 3 of "Disgust" were identical to this, except they state the following: "...and express your DISGUST one more time" (Trial 2); "....and express your DISGUST one last time" (Trial 3).*

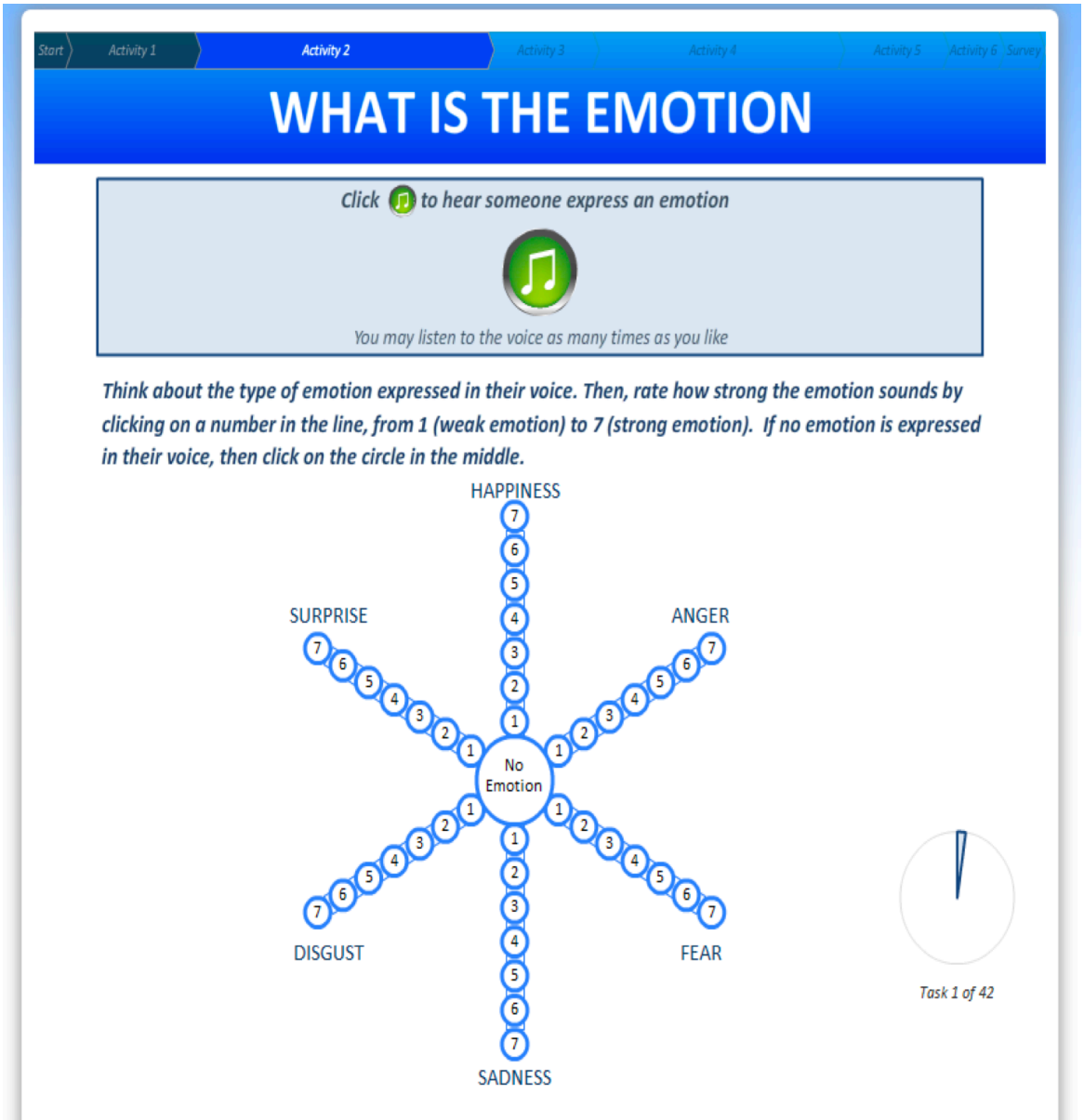
III. Emotion Recognition

This task includes a 7-alternative forced-choice recognition paradigm, where participants are instructed to classify stimuli from a validated battery of vocal affect bursts ("Montreal Affective Voices" [MAV]; Belin et al., 2008) into one of the six basic emotion categories or a neutral category ("No Emotion"). For stimuli labelled as an emotion, participants are also required to rate its intensity on a Likert-type scale of *1 = weak* to *7 = strong*. Stimuli labelled as being neutral are automatically assigned an emotional intensity rating of *0*. There are six stimuli (3 male, 3 female) for each of the seven categories, yielding a total of 42 trials (maximum accuracy score = 42). Trials are randomised across participants. **This task is described in more detail in Studies 1-3 (Chapters 5-7).**

Task overview



Task interface

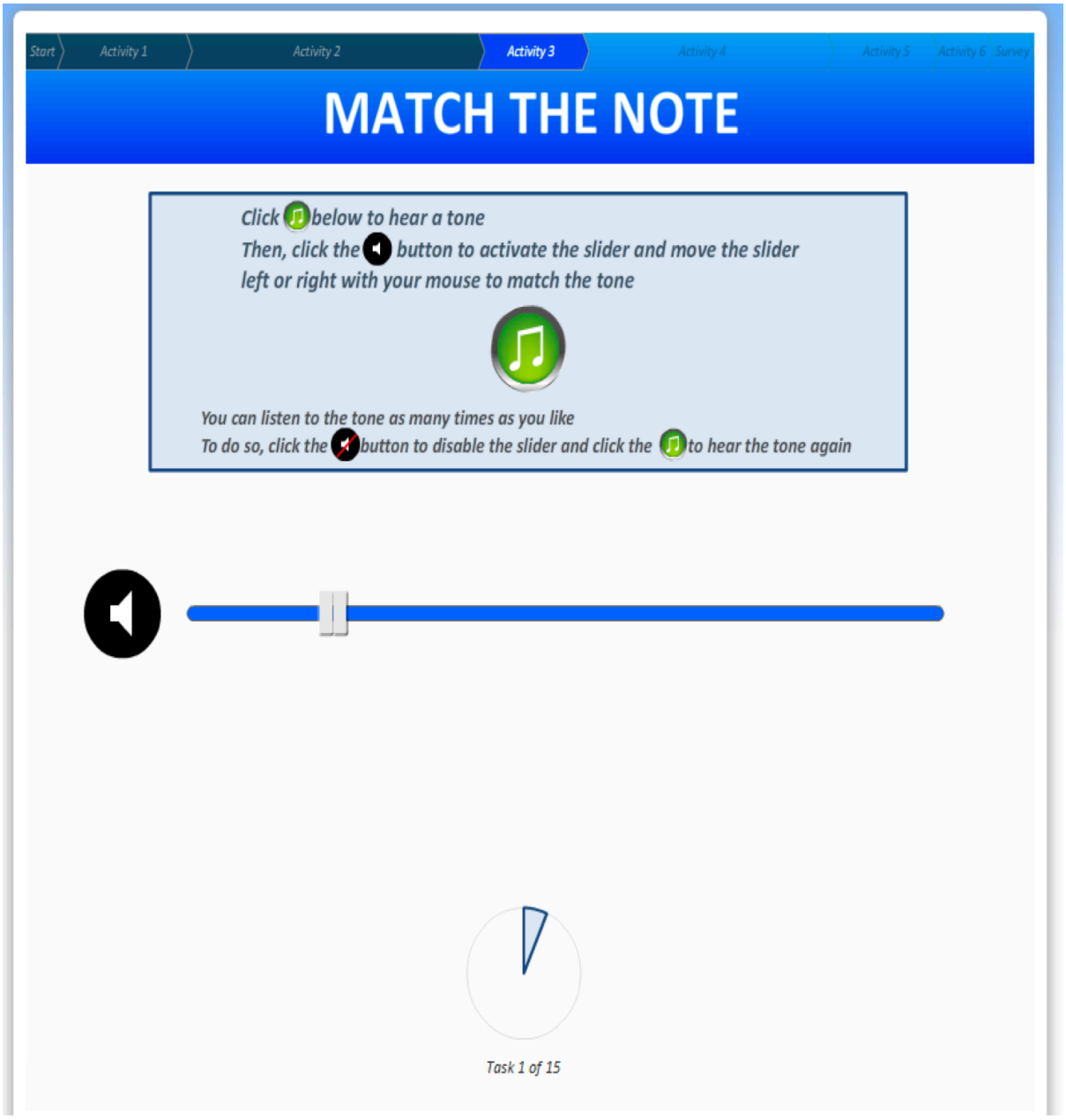


**The position of the six basic emotion categories is randomised around the "wheel" after every seven trials.*

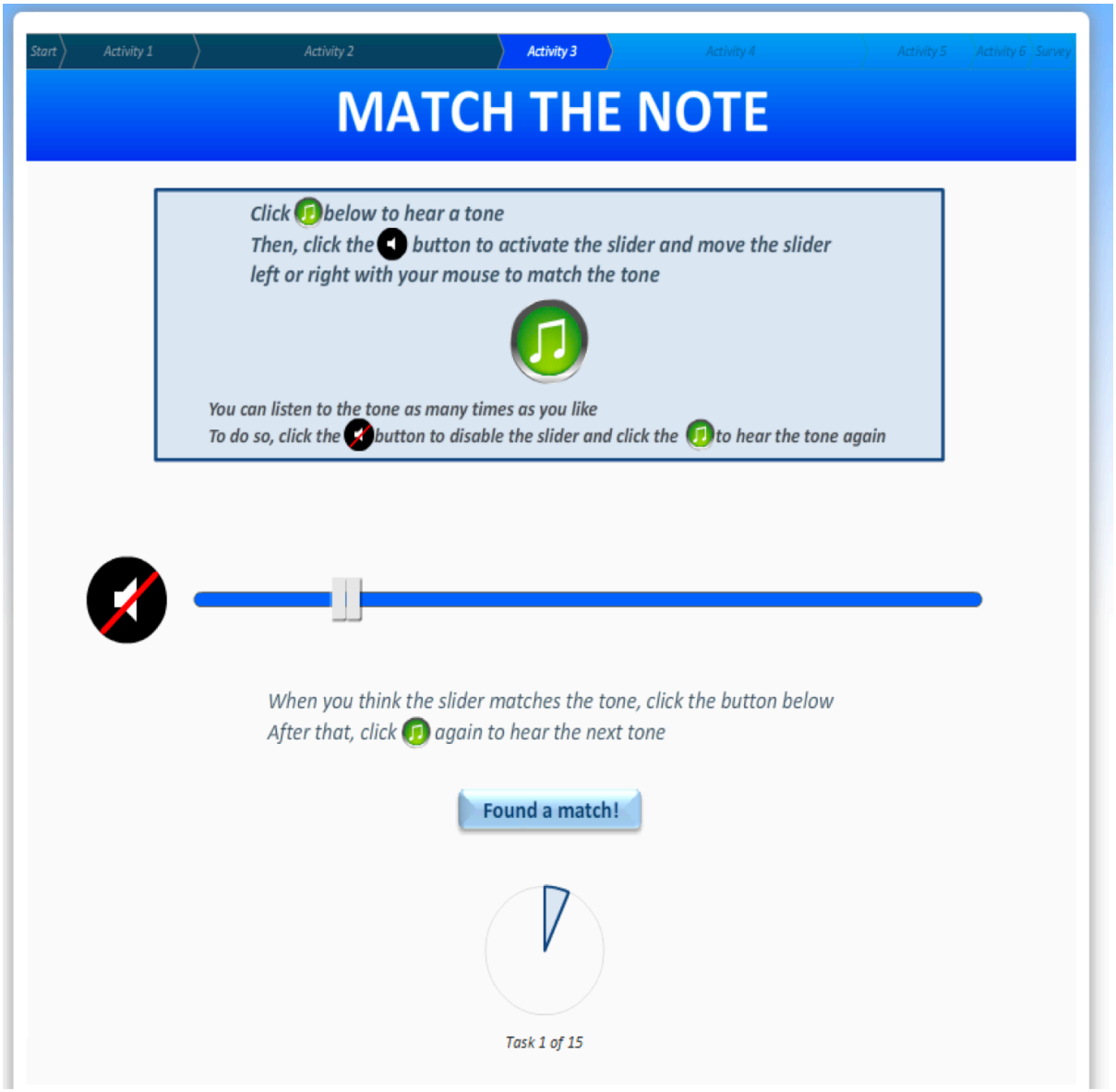
IV. Pitch Processing Task 1: "Match the Note"

Participants are required to match complex tones of five different fundamental frequencies (F0) to a sine tone on a pitch "slider". Males and females have different target F0s to match. Each tone is presented three times (15 total trials). Trials are randomised across participants. **Male F0:** 123.47 Hz, 138.59 Hz, 155.56 Hz, 174.61 Hz, 196.0 Hz. **Female F0:** 246.94 Hz, 277.18 Hz, 311.13 Hz, 349.23 Hz, 392.0 Hz.

Step 1



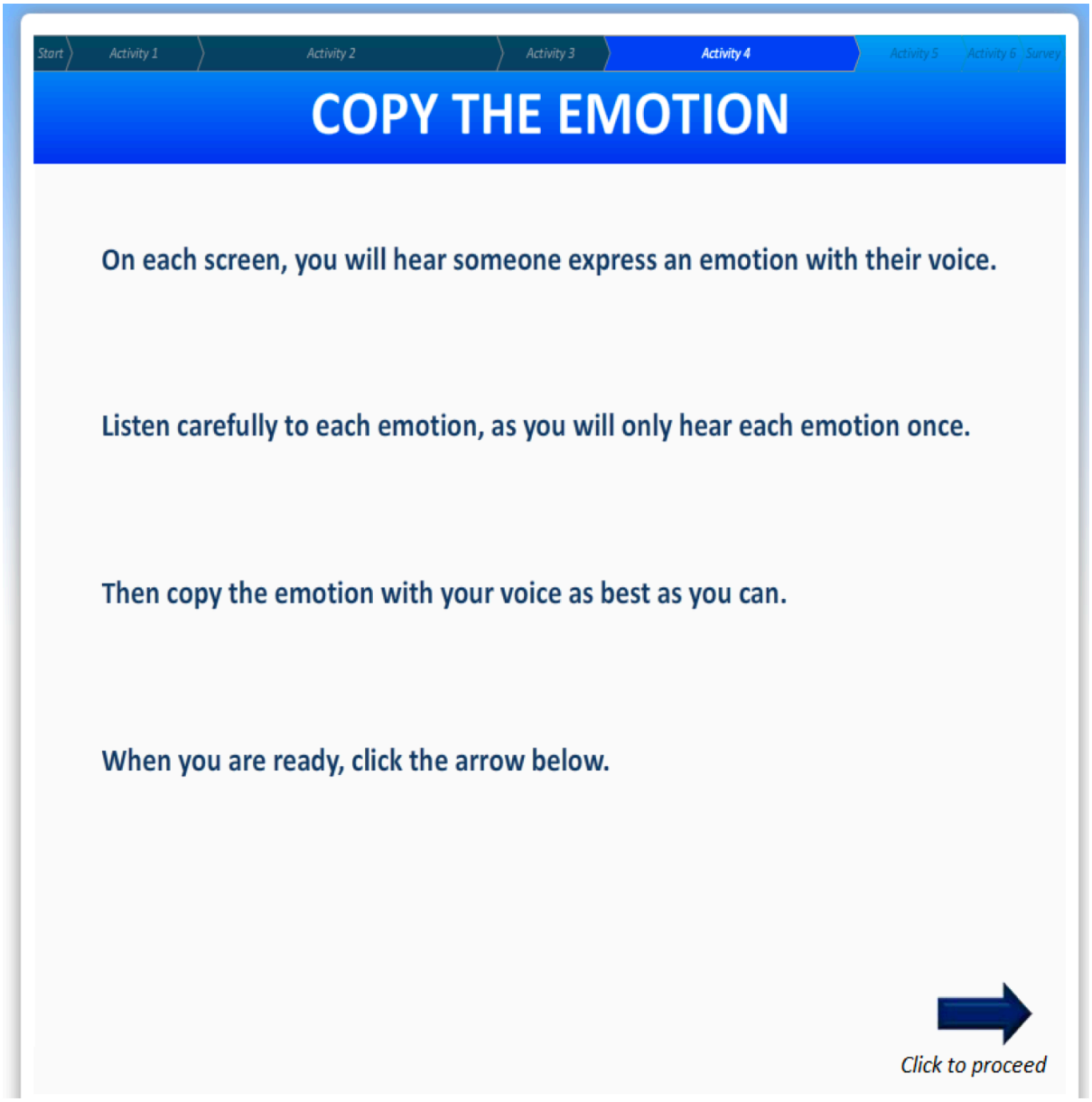
Step 2


Start
Activity 1
Activity 2
Activity 3
Activity 4
Activity 5
Activity 6
Survey
MATCH THE NOTE
Click below to hear a tone
Then, click the button to activate the slider and move the slider
left or right with your mouse to match the tone
You can listen to the tone as many times as you like
To do so, click the button to disable the slider and click the to hear the tone again
When you think the slider matches the tone, click the button below
After that, click again to hear the next tone
Found a match!
Task 1 of 15

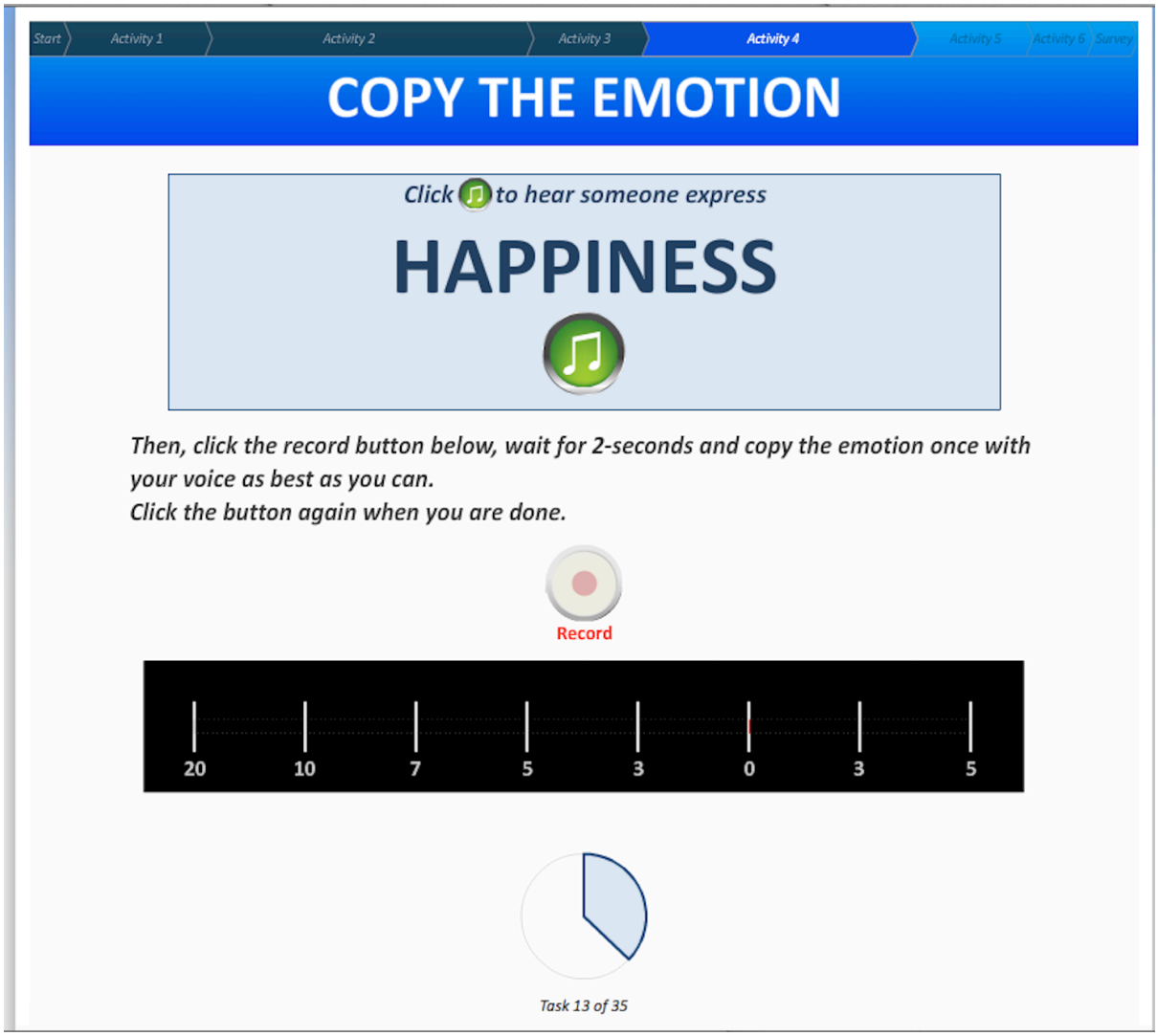
V. Emotion Imitation

Participants are required to imitate stimuli from the MAV representing the six basic emotions and the neutral category. Participants are expected to imitate voices from the same sex. There are five stimuli per category to imitate (35 trials in total). Trials are randomised across participants.

Task overview

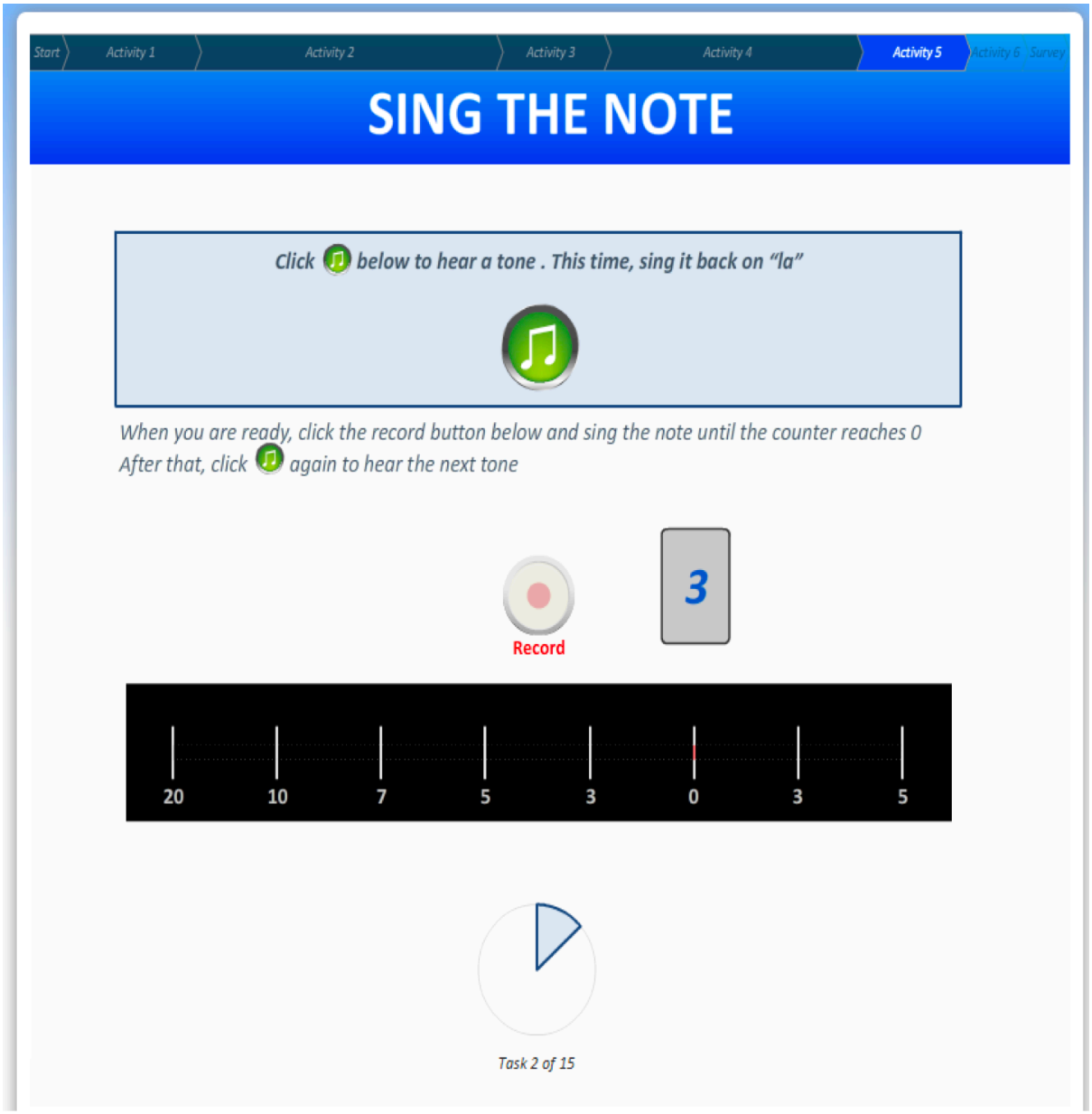


Task interface



VI. Pitch Processing Task 2: "Sing the Note"

Participants are required to match the pitch of a complex tone with their voice. Males and females have different target pitches to match (same tones as those presented in the "Match the Note" task). Each tone is presented three times (15 total trials) in randomised order. **Male F0:** 123.47 Hz, 138.59 Hz, 155.56 Hz, 174.61 Hz, 196.0 Hz. **Female F0:** 246.94 Hz, 277.18 Hz, 311.13 Hz, 349.23 Hz, 392.0 Hz.

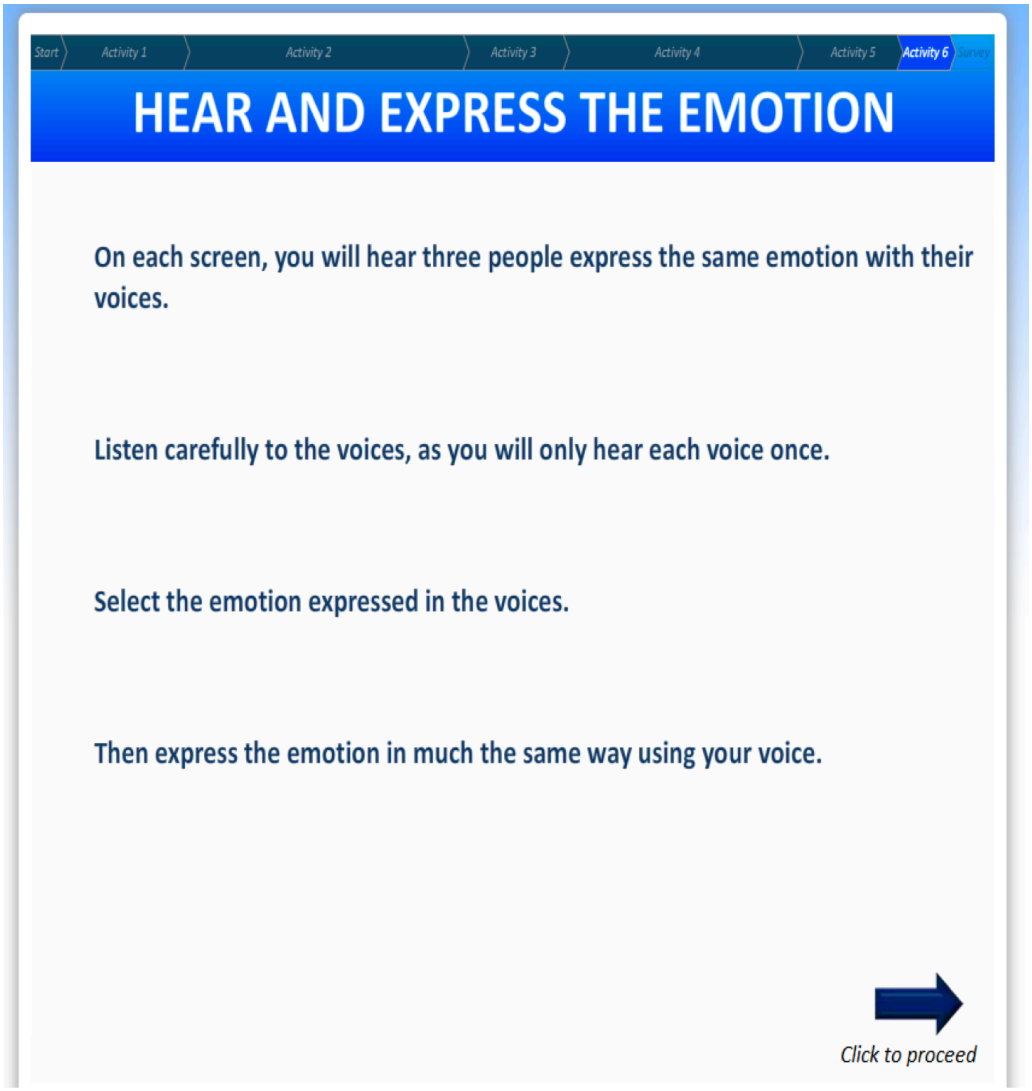


**The number besides the record button represents the 3 s that participants are given to sing the note.*

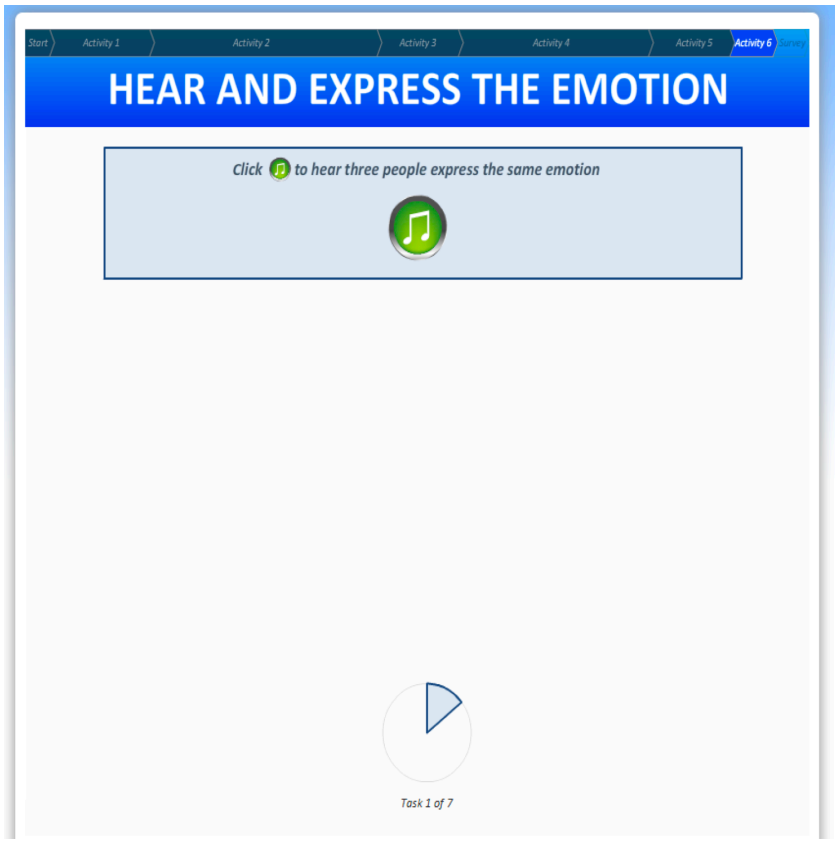
VII. Hear and Express the Emotion

On each trial, participants listen to three voices (expressed by different actors) from the MAV that correspond to a single basic emotion category or the neutral category. The three stimuli per emotion have similar acoustic features. Next, participants select the emotion (or neutral category) in the voice from seven alternatives. Finally, they are required to imitate the emotion once with their own voice (e.g., not to imitate each of the three voices they heard). This task assesses whether participants can capture and simulate the "signature" (e.g., roughness in the voice for growls of anger; brief onset in gasps of surprise) of the emotion they heard in the voice. There are seven trials in total (one per emotion), randomised across participants.

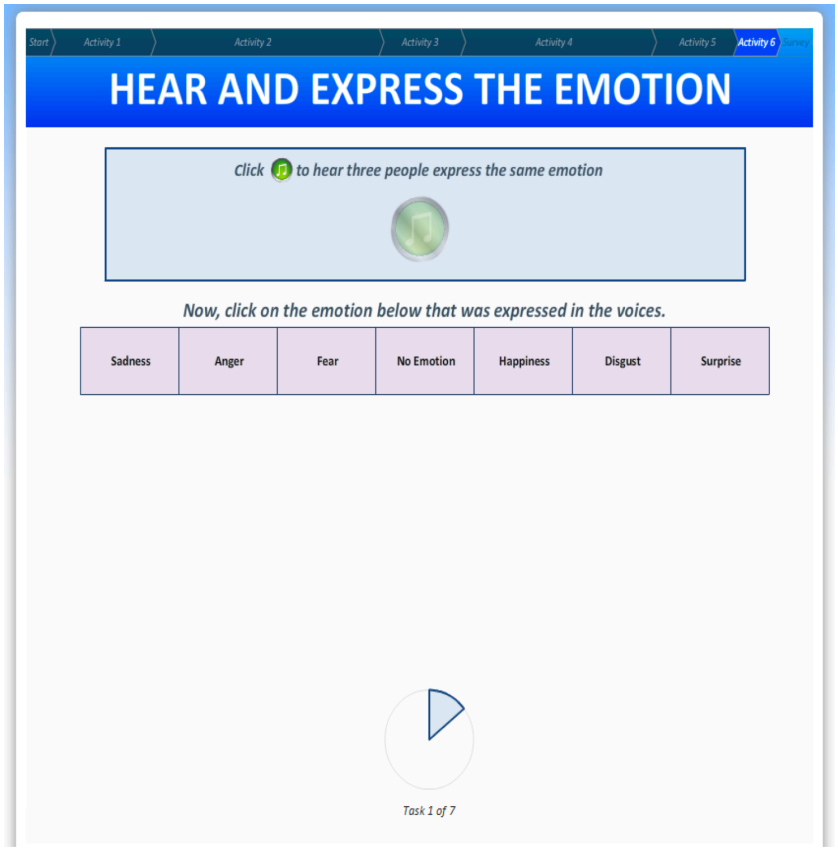
Task overview



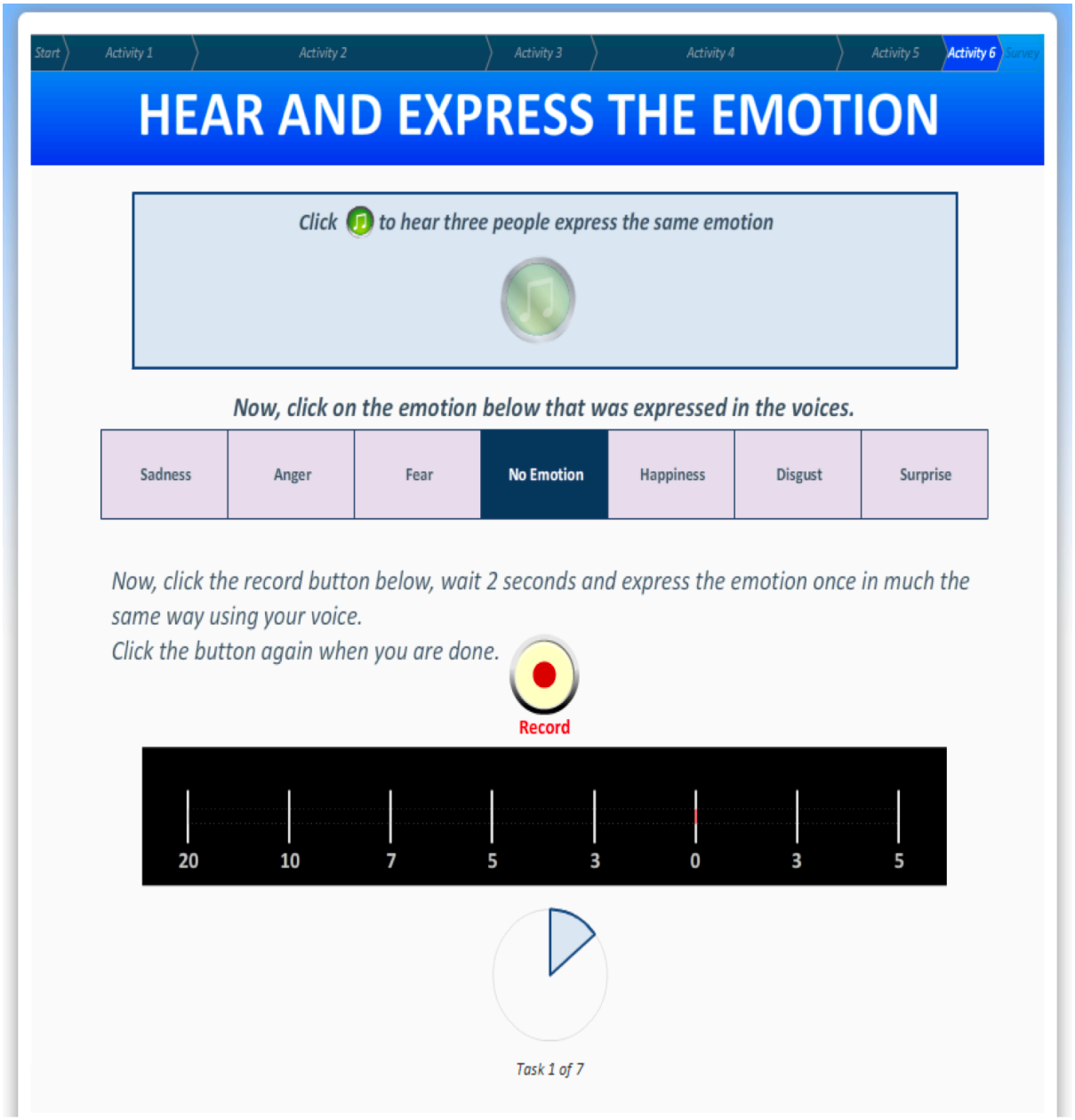
Step 1


Start
Activity 1
Activity 2
Activity 3
Activity 4
Activity 5
Activity 6
Survey
HEAR AND EXPRESS THE EMOTION
Click to hear three people express the same emotion
Task 1 of 7

Step 2

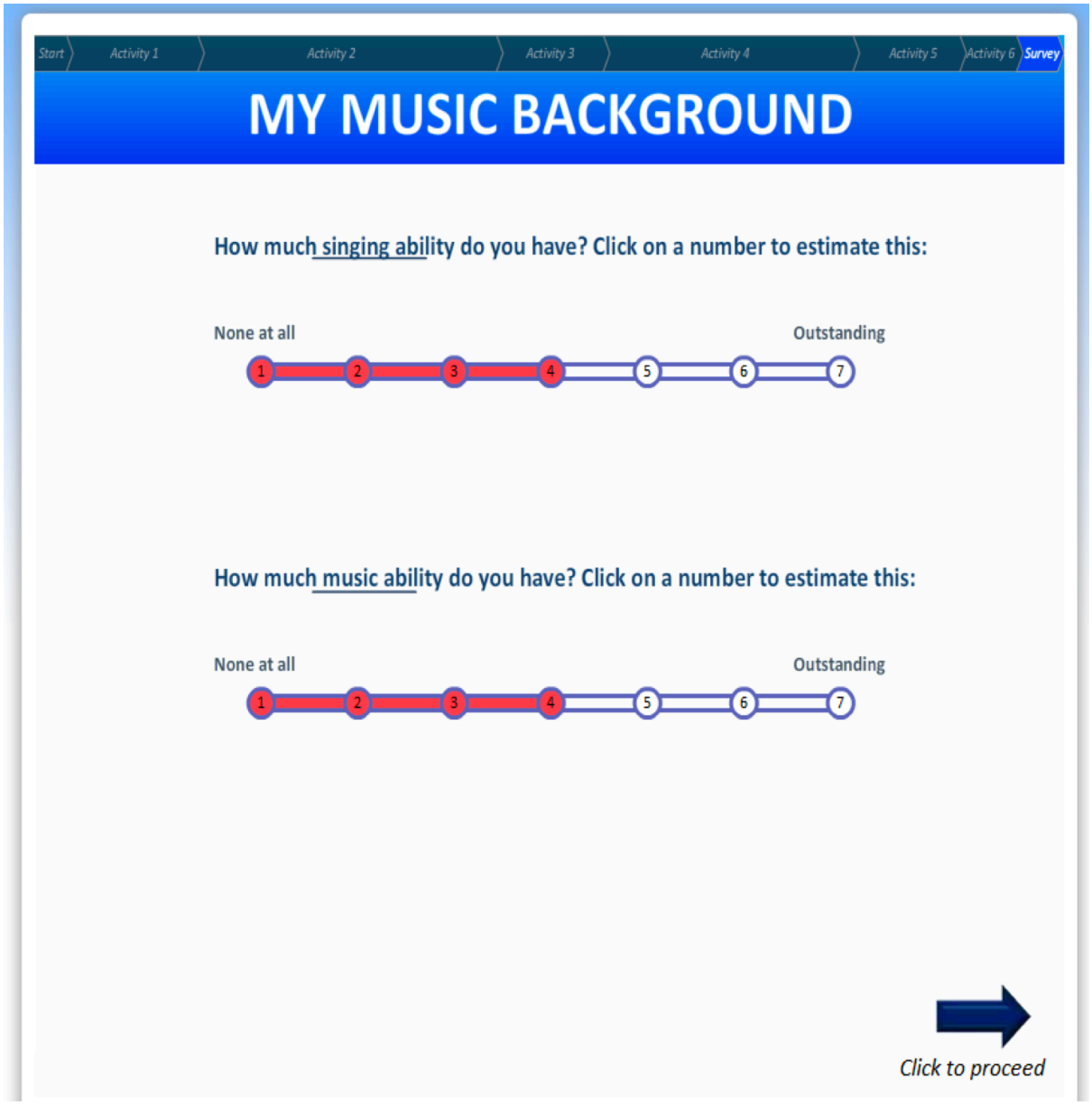

Start
Activity 1
Activity 2
Activity 3
Activity 4
Activity 5
Activity 6
Survey
HEAR AND EXPRESS THE EMOTION
Click to hear three people express the same emotion
Now, click on the emotion below that was expressed in the voices.
Sadness
Anger
Fear
No Emotion
Happiness
Disgust
Surprise
Task 1 of 7

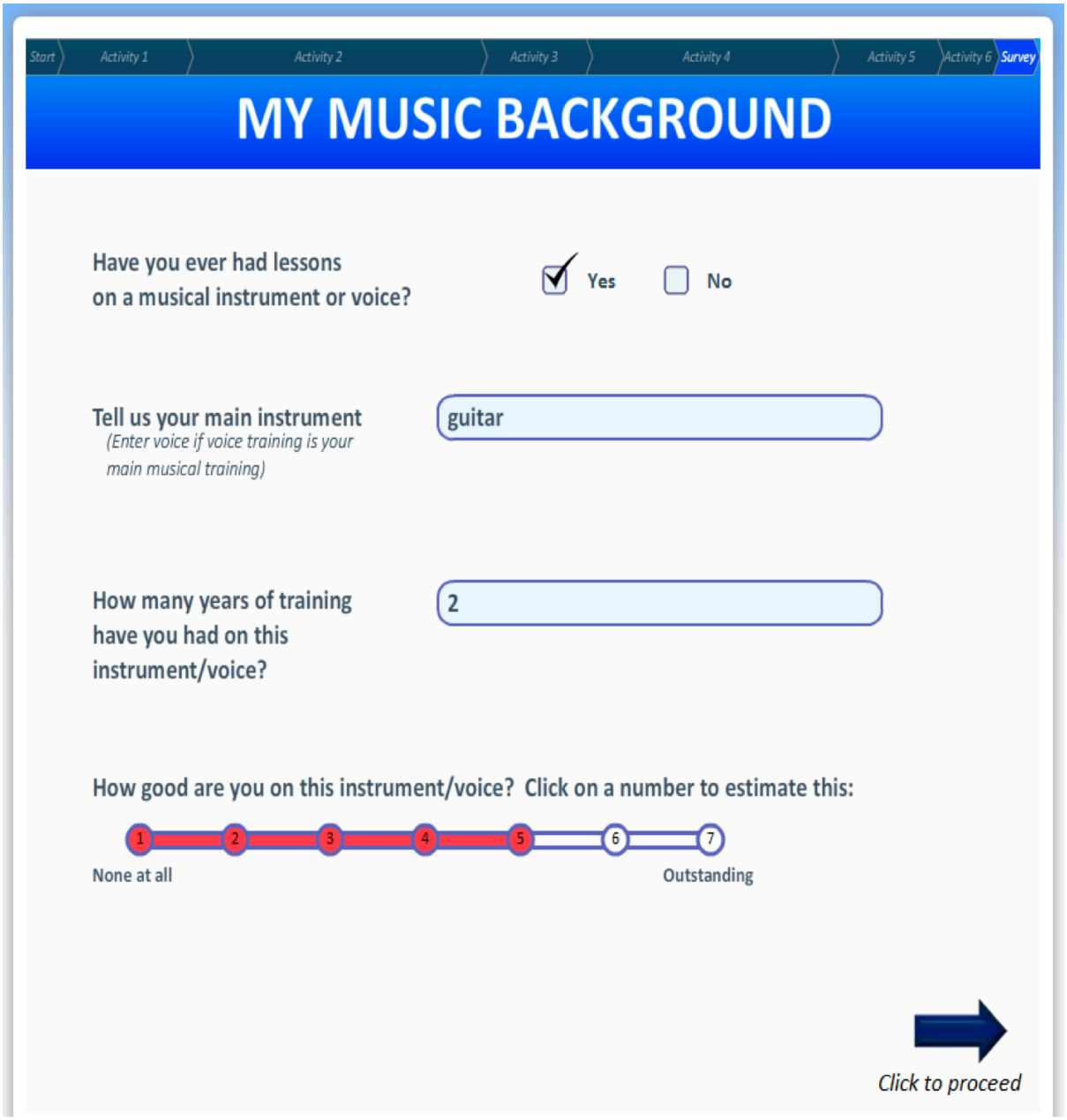
Step 3


Start
Activity 1
Activity 2
Activity 3
Activity 4
Activity 5
Activity 6
Survey
HEAR AND EXPRESS THE EMOTION
Click to hear three people express the same emotion
Now, click on the emotion below that was expressed in the voices.
Sadness
Anger
Fear
No Emotion
Happiness
Disgust
Surprise
Now, click the record button below, wait 2 seconds and express the emotion once in much the same way using your voice.
Click the button again when you are done.
Record
20
10
7
5
3
0
3
5
Task 1 of 7

VIII. Music Questionnaire

Participants provide information about their musical background. Examples of responses are indicated below:




Start
Activity 1
Activity 2
Activity 3
Activity 4
Activity 5
Activity 6
Survey
MY MUSIC BACKGROUND
Have you ever had lessons on a musical instrument or voice?
Yes
No
Tell us your main instrument
(Enter voice if voice training is your main musical training)
guitar
How many years of training have you had on this instrument/voice?
2
How good are you on this instrument/voice? Click on a number to estimate this:
1
2
3
4
5
6
7
None at all
Outstanding
Click to proceed


Start
Activity 1
Activity 2
Activity 3
Activity 4
Activity 5
Activity 6
Survey
MY MUSIC BACKGROUND
Some people are able to name a musical sound just from hearing it.
For example, they can hear a musical note and tell if it's a G, or an E-flat.
This is called "perfect pitch". Very few people have perfect pitch.
Do you have perfect pitch?
Yes
No
Doe anyone in your family have perfect pitch?
Yes
No
Who has perfect pitch?
(Example: mother, brother)
dad
Click to proceed

Appendix B

Systemising in ASD

This appendix provides an overview of the "systemising" component of the Empathising-Systemising hypothesis of ASD (Baron-Cohen, 2009), to supplement the review of empathising in Section 3.3:

The concept of systemising was introduced by Baron-Cohen (2002) to describe a drive to construct systems and analyse how they work. Here, a "system" refers to "something that takes inputs, which can then be operated on in *variable* ways, to deliver *different* outputs in a rule-governed way" (p. 361; Baron-Cohen et al., 2003). One can predict the behaviour of a system by drawing "if-then" associations between the operation and output (e.g., "*x* always causes *y*", or "if I do *x*, then *y* should happen"), provided that the evidence is precise and consistent. Systemising relates to phenomena that follow a constant pattern, are highly predictable and ultimately fact-based (e.g., laws of nature, language syntax, mathematical formulae, workings of a machine; Baron-Cohen, 2009; Baron-Cohen et al., 2003).

Individuals with ASD have intact or superior systemising skills relative to controls (i.e., "hyper-systemising"), as exemplified in part by their excellent attention to detail, which also supports the weak central coherence theory of ASD (Frith & Happé, 1994; Happé & Frith, 2006). There is consistent evidence to show that they perform better than controls on the Embedded Figures Task (i.e., high accuracy and/or speed), which requires participants to identify simple figures within a large complex design (Jarrold, Gilchrist, & Bender, 2005; Jolliffe & Baron-Cohen, 1997; Ropar & Mitchell, 2001; Shah & Frith, 1983). They also demonstrate strong performance on visual search tasks (Jarrold et al., 2005; O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001; Plaisted, O'Riordan, & Baron-Cohen, 1998) and the Wechsler Block Design task where segmenting a gestalt into its constituent blocks aids construction of the design (Ropar & Mitchell, 2001; Shah & Frith, 1993). A local-processing bias is important for systemising because it predisposes individuals to attend to parts of a system in order to predict how it behaves as a coherent whole (Baron-Cohen, Ashwin, Ashwin, Tavassoli, & Chakrabarti, 2009). This view contradicts the weak central coherence theory,

which generally considers a detail-focused cognitive style to be disadvantageous for integrating information in context and understanding the "big picture" (Baron-Cohen, 2009; Happé & Frith, 2006).

Hyper-systemising also accounts for repetitive behaviours and insistence on sameness in ASD, as individuals develop routines and rituals to impose structure and predictability to their world (Baron-Cohen et al., 2009). In addition to motor stereotypies (e.g., rocking, unusual hand/finger movements), examples of repetitive behaviours in ASD include spinning objects, arranging things in rows or patterns until they are "just right", insisting that belongings always be kept in the same place, eating the same food at every meal, and adhering to a strict daily routine (Barrett et al., 2015; Dewrang & Sandberg, 2011; Lam & Aman, 2007). Studies have shown associations between the severity of repetitive behaviours and executive dysfunction in ASD, including poor cognitive flexibility and behavioural inhibition (Boyd, McBee, Holtzclaw, Baranek, & Bodfish, 2009; Lopez, Lincoln, Ozonoff, & Lai, 2005; Miller, Ragozzino, Cook, Sweeney, & Mosconi, 2015). However, unlike hyper-systemising, the theory of executive dysfunction in ASD (Hill, 2004; Hughes, Russell, & Robbins, 1994) views repetitive behaviours as perseverative and maladaptive (e.g., unable to interrupt behaviour even when they want to) and cannot account for cases in which good understanding of a system is achieved through repetition (Baron-Cohen, 2009).

Individuals with ASD also have intense circumscribed interests or hobbies centred on machines and other systemisable domains. Using a parent-report questionnaire, Baron-Cohen and Wheelwright (1999) found that children with ASD had more "obsessions" that clustered in the domain of "folk physics" (e.g., knowledge of how objects work; machines, computers, vehicles, astronomy, building Lego) than "folk psychology" (e.g., knowledge of how the social world works; imagination, relationships, gossip, beliefs) compared to a control group of children with Tourette's Syndrome. Other areas of strong interest in the ASD group included biology, mathematics, taxonomy (e.g., collecting, categorising), and video/audio. Similar findings have been reported in other survey-based studies (Caldwell-Harris & Jordan, 2014; Klin, Danovitch, Merz, & Volkmar, 2007; Turner-Brown, Lam, Holtzclaw, Dichter, & Bodfish, 2011) and in one study assessing the content of special interests in through internet forum posts (Jordan & Caldwell-Harris, 2012). Further, high-functioning adults with ASD tend to pursue a university education in the fields of science, technology, engineering, or mathematics (STEM) compared to non-STEM fields (Wei et al., 2014; Wei, Yu, Shattuck,

McCracken, & Blackorby, 2013). One study also found that the longest attained professions of high-functioning adults with ASD involved more technical skills (e.g., software engineers, mechanics) than those of adults with schizophrenia or healthy controls (Spek & Velderman, 2013).

Evidence for hyper-systemising in ASD is also drawn from studies showing higher self- or informant-report on the Systemising Quotient (SQ) for children, adolescents, and adults with ASD compared to controls (Auyeung et al., 2012; Auyeung et al., 2009; Baron-Cohen et al., 2003). In the general population, males score higher on the SQ compared to females, although sex differences are not observed in ASD groups (Auyeung et al., 2012; Auyeung et al., 2009; Baron-Cohen et al., 2003; Wakabayashi, Baron-Cohen, Wheelwright, et al., 2006). Hyper-systemising in ASD therefore supports the "extreme male brain" theory of ASD (an extension of the E-S theory), which claims that individuals with ASD tend to have a "hyper-masculinised" profile (i.e., high systemising, low empathy) regardless of sex (Auyeung et al., 2012; Auyeung et al., 2009; Baron-Cohen, 2002). Consistent with this theory, studies on the general population have also shown that males score higher (e.g., more ASD-related traits) than females on the AQ (Baron-Cohen, Hoekstra, Knickmeyer, & Wheelwright, 2006; Baron-Cohen et al., 2001), and that higher AQ scores correlate with higher SQ scores but lower scores on the Empathy Quotient (Baron-Cohen et al., 2003; Wheelwright et al., 2006). Further, more males work or study in the fields of IT, technology and exact sciences (e.g., physics), while more females gravitate towards psychology, education, social sciences and humanities (Svedholm-Häkkinen & Lindeman, 2016).

Researchers have designed intervention programs for ASD that draw on strengths in systemising to facilitate empathy, specifically emotion recognition (Golan et al., 2010; Golan & Baron-Cohen, 2006). These include interactive computerised interventions, which are considered to be effective and motivating likely because they appeal to those interested in technical systems and provide a controlled, predictable environment for learning (Wainer & Ingersoll, 2011). One example is the "Mind Reading" software, which facilitates the recognition of complex emotions or mental states expressed in the face and voice (Golan & Baron-Cohen, 2006). Emotions are demonstrated in videos, voice recordings, and written examples of emotional contexts, grouped into 24 broader emotion groups. Users are able to learn each emotion at their own pace or through in-built lesson plans, quizzes and games, which come with rewards for correct answers (e.g., user presented with facts/photos of trains for

positive reinforcement). High-functioning adults with ASD who used the software independently or in group tutorials were better at recognising emotions after 10-15 weeks, although this was limited to stimuli from the program and not generalised to unfamiliar emotional stimuli (Golan & Baron-Cohen, 2006). This intervention was also effective in high-functioning children, who were able to generalise emotion recognition skills to unfamiliar voices but not faces (Lacava, Golan, Baron-Cohen, & Smith Myles, 2007).

Another example is the "Transporters" DVD, which teaches children with ASD how to recognise 15 age-appropriate basic and complex emotions, using photos of human faces grafted on vehicles that move in a predictable manner (e.g., trains, cable cars, tractors; Golan et al., 2010). Parents are encouraged to let their children watch the DVD repeatedly and to facilitate discussion about the causes and consequences of each emotion after each episode. Studies have found that after 3-4 weeks, high-functioning children showed improvement in emotion recognition ability, not just for faces included in the DVD, but also for unfamiliar faces which were not attached to vehicles (Golan et al., 2010; Young & Posselt, 2012). However, the intervention has limited benefits on children with ASD and comorbid intellectual disability, as one study showed improvement in the recognition of anger alone, which was not maintained at follow-up three months later (Williams et al., 2012).

APPENDIX C

Behavioural Studies Assessing the Recognition of Vocal Emotions in ASD

This appendix supplements the review on emotional voice processing in ASD in Chapter 4. It presents a summary of studies (N = 34) assessing the recognition of emotional voices (basic emotions only) in ASD. Studies were selected from a recent search of the following terms (title or abstract) on the PyscINFO and PubMed databases: "autism", "voice" (or "vocal"), and "emotion". The majority of studies in the table below pertain to the recognition of speech-embedded prosody, with a smaller number of studies assessing the recognition of non-linguistic emotional vocalisations (vocal affect bursts). Studies are arranged in chronological order according to the year of publication. Refer to the "Note" below the table for supplementary information.

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
*Hobson (1986)	Three groups Group 1: - *n* = 23 (18:5) - M_{age} = 14 yr, 7 mo (34 mo) - Low VIQ Group 2: - *n* = 11 - M_{age} = 14 yr, 5 mo (24 mo) - Low VIQ Group 3: - *n* = 15 - M_{age} = 14 yr, 9 mo (33 mo) - Low VIQ	Three groups Group 1 (TD): - *n* = 23 (15:8) - M_{age} = 7 yr, 3 mo (21 mo) - Match with ASD Group 1 on PIQ Group 2 (ID): - *n* = 11 - M_{age} = 14 yr, 0 mo (22 mo) - Match with ASD Group 2 on PIQ Group 3 (TD): - *n* = 15 - M_{age} = 7 yr, 1 mo (15 mo) - TD - Match with ASD Group 3 on VIQ	Anger, fear, happiness, sadness ("unhappy"), neutral	Stimuli: **vocal affect bursts** Task: cross-modal matching (voice to line drawings of facial emotions) Other task: cross-modal matching (non-emotional sounds to visual objects/scenes)	**ASD (all 3 groups) < Controls (all 3 groups)**: [b] total emotion **ASD = Controls**: non-emotional sounds
*Gioia and Brosgole (1988)	Two groups Moderate ID: - *n* = 7 (all males) - Mdn_{age} = 13 yr, 10 mo	Three groups TD: - *n* = 10 (5:5) - *Range* = 5 yr 4 mo – 6 yr 1 mo	Anger, happiness, sadness	Stimuli: emotional prosody in sentences with neutral content Task: forced-choice emotion labelling; cross-modal	**ASD (all groups) < TD**: total emotion (emotion labelling and cross-modal matching to faces and postures)

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
	Severe ID: - *n* = 8 (all males) - Mdn_{age} = 17 yr, 5 mo	Moderate ID: - *n* = 9 (7:2) - Mdn_{age} = 17 yr, 6 mo Severe ID: - *n* = 8 (4:4) - Mdn_{age} = 19 yr, 1 mo		matching to facial emotions or emotional body postures	**ASD (all groups) = Controls (moderate and severe ID)**
Hobson et al. (1988)	- *n* = 21 (18:3) - M_{age} = 18 yr, 9 mo (45 mo) - Low receptive vocabulary scores	- *n* = 21 (16:5) - M_{age} = 18 yr, 5 mo (47 mo) - TD - Match on receptive vocabulary scores	Anger, disgust, fear, happiness, sadness ("unhappy"), surprise	Stimuli: emotional prosody in short passages with neutral verbal content; **vocal affect bursts** Task: cross-modal matching (prosody to photos of emotional faces) Other task: cross-modal matching (non-emotional sounds to pictures of objects/scenes)	**ASD = TD**: total emotion (in prosody and vocal affect bursts) **ASD < TD**: more ASD difficulty recognising emotional voices vs. non-emotional sounds
Hobson et al. (1989)	- *n* = 21 (18:3) - M_{age} = 18 yr, 9 mo (45 mo) - Low receptive vocabulary scores	Two groups ID: - *n* = 21 (16:5) - M_{age} = 18 yr, 5 mo (47 mo) - Matched on receptive vocabulary scores	Anger, disgust, fear happiness, sadness ("unhappy"), surprise	Stimuli: emotional prosody in short passages with neutral verbal content; **vocal affect bursts** Task: forced-choice emotion labelling	**ASD < TD and ASD < ID**: total emotions (in prosody and vocal affect bursts) **ASD = TD and ID**: non-emotional sounds

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
		TD: - *n* = 21 (13:8) - M_{age} = 7 yr, 2 mo (23 mo) - Match on receptive vocabulary scores		Other task: labelling non-emotional sounds	
Macdonald et al. (1989)	- *n* = 10 (all males) - M_{age} = 27.2 (5.6) - HFA	- *n* = 10 (all males) - M_{age} = 26.2 (2.9) - TD - Match on PIQ	Anger, fear, happiness, sadness	Stimuli: emotional prosody in sentences with neutral verbal content and filtered sentences (so content is unintelligible) Task: forced-choice emotion labelling	**ASD < TD**: total emotion
*van Lancker et al. (1989)	Two groups (total *n* = 28) Younger (< 8 yr): - M_{age} = 6.9 (1.2) - Low mental age Older (> 8 yr): - M_{age} = 11.3 (3.1) - Low mental age	Two groups (total *n* = 33) Younger TD - M_{age} = 5.3 (1.4) Older TD - M_{age} = 11.2 (2.5)	Anger, happiness, sadness, surprise	Stimuli: emotional prosody in sentences with neutral verbal content Task: forced-choice emotion labelling Other task: linguistic task – match line drawing to verbal content of speech	**ASD < TD**: total emotion **ASD = TD**: linguistic task
*Ozonoff, Pennington, and Rogers (1990)	- *n* = 14 (10:4) - M_{age} = 6.40 (2.04) - Low verbal mental age	- *n* = 14 (10:4) - M_{age} = 3.00 (0.27) - Matched on verbal mental age	Anger, happiness, sadness	Stimuli: **vocal affect bursts**	**ASD < TD**: total emotion **ASD = TD**: non-emotional sounds

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
				Task: cross-modal matching (match photographs of emotional faces to voice) Other task: cross-modal matching (non-emotional sounds to visual objects/scenes)	
*Prior, Dahlstrom, and Squires (1990)	- *n* = 20 (14:6) - M_{age} = 9 yr, 11 mo - Low verbal mental age on average (although 6 had normal verbal IQ) -	- *n* = 20 (14:6) - M_{age} = 10 yr - Matched on verbal mental age	Anger, fear, happiness, sadness, neutral	Stimuli: **vocal affect bursts** Task: cross-modal matching (match drawings of emotional faces to voice) Other task: cross-modal matching (non-emotional sounds to visual objects/scenes)	**ASD = TD**: total emotion, non-emotional sounds
Loveland et al. (1995)	- *n* = 28 (22:6) - M_{age} = 145 mo (61.1) - Low verbal and non-verbal mental age	- *n* = 30 (12:18) - M_{age} = 158.6 mo (60.7) - Down Syndrome (DS)	Anger, happiness, sadness, surprise, neutral	Stimuli: emotional prosody in vocal track presented in/out-of-sync with two videos (split-screen) of people reading scripts aloud with facial expressions. One video portrayed the target emotion in verbal content of the speech and facial expression, and the other video portrayed a	**ASD < DS**: total emotion (particularly when synchrony between vocal track and video was reduced) **ASD = DS**: non-emotional sounds

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
				different emotion in speech and face. Task: cross-modal matching (pick which video fits emotional prosody in vocal track) Other task: cross-modal matching (pick which one of two videos of objects/non-emotional events match non-emotional sound)	
*Lindner and Rosén (2006)	- *n* = 14 (12:2) - M_{age} = 10.20 yr (2.89) - AS	- *n* = 16 (11:5) - M_{age} = 10.19 yr (3.12) - TD - Match on receptive vocabulary scores	Anger, happiness, sadness, neutral	Stimuli: emotional prosody in short passages with neutral verbal content Task: cross-modal matching (prosody to pictures of emotions with verbal labels)	**ASD < TD**: total emotion
*Mazefsky and Oswald (2007)	Two groups AS: - *n* = 16 - M_{age} = 11.47 (2.06) HFA: - *n* = 14	No controls—AS and HFA performance compared to TD norms on standardised test	Anger, fear, happiness, sadness	Stimuli: emotional prosody in sentences; prosody varies from low to high intensity Task: forced-choice emotion labelling	**HFA < TD norms**: total emotion (regardless of cue intensity) **AS = TD norms**

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
	- M_{age} = 11.00 (2.66)				**HFA < AS**: recognition total emotion with low intensity
Kahana-Kalman and Goldman (2008)	- *n* = 18 (15:3) - M_{age} = 49 mo (*SD* not specified) - Low mental age	- *n* = 18 (11:7) - M_{age} = 44 mo (*SD* not specified) - TD	Anger, happiness, sadness	Stimuli: emotional voice (not specified if emotional prosody or vocal affect bursts) coupled with two videos of facial emotions presented simultaneously. Emotional voice only matches one of the two faces. Stimuli produced by child's mother or stranger. Task: cross-modal matching (pick which one of the two faces matches the emotional voice). Use eye gaze tracking to measure preferentially looking as index of emotion recognition Other task: cross-modal matching (pick which one of two videos of objects/non-emotional events match a non-emotional sound; eye gaze tracking)	**ASD < TD**: total emotion (stranger's voice) **ASD < TD**: sadness (mother's voice) **ASD = TD**: non-emotional sounds

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
Baker et al. (2010)	- *n* = 19 (13:6) - M_{age} = 12.80 (1.47) - HFA	- *n* = 19 (13:6) - M_{age} = 12.20 (1.43) - TD	Anger, happiness, sadness, neutral	Stimuli: emotional prosody in "nonsense" sentences Task: forced-choice emotion labelling on a dichotic listening task	**ASD = TD**
*Philip et al. (2010)	- *n* = 23 (16:7) - M_{age} = 32.50 (10.90) - AS/HFA	- *n* = 23 (17:6) - M_{age} = 32.40 (11.10) - TD	Anger, disgust, fear, happiness, sadness	Stimuli: emotional prosody in string of numbers Task: forced- choice emotion labelling	**ASD < TD**: anger, disgust, fear, happiness
Brennand et al. (2011)	- *n* = 15 (14:1) - M_{age} = 14.50 (2.70) - AS	Two groups of TD Group 1 (school-aged): - *n* = 15 (12:3) - M_{age} = 13.30 (1.67) Group 2 (undergrad): - *n* = 32 (28:4) - M_{age} = late teens, early twenties	Anger, fear, happiness, sadness	Stimuli: emotional prosody in "nonsense" sentences Task: forced-choice emotion labelling	**ASD < TD (group 2)**: total emotion **ASD = TD (group 1)**
Jones et al. (2011)	Two groups LFA (IQ < 80): - n = 40 (35:5) - M_{age} = 15 yr, 6 mo (5.0)	Two groups LFC (IQ < 80): - n = 23 (20:3) - M_{age} = 15 yr, 5 mo (4.1)	Anger, disgust, fear, happiness, sadness, surprise	Stimuli: emotional prosody in three-digit numbers; **vocal affect bursts** Task: forced-choice emotion labelling	**ASD (both groups) = Controls (both groups)**: for total emotion recognition across modalities (SEM modelling of emotion

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
		- Match to LFA on FSIQ, VIQ, PIQ		Other task: facial emotion recognition	recognition ability as a multimodal construct rather than independent unimodal components)
	HFA (IQ > 80): - n = 59 (55:4) - M_{age} = 15 yr, 6 mo (6.0)	HFC (IQ > 80): - n = 34 (all males) - M_{age} = 15 yr, 7 mo (6.9) - Match to HFA on FSIQ, VIQ, PIQ			**Low IQ (ASD + controls) < High IQ (ASD + controls)**: total emotion recognition across modalities
*Vannetzel et al. (2011)	- *n* = 10 (9:1) - M_{age} = 9.6 (1.7) - PDD-NOS	- *n* = 25 (20:5) - M_{age} = 8.4 (1.8) - TD	Anger, happiness, sadness, neutral	Stimuli: **vocal affect bursts** Task: same/different emotion judgments for unimodal (voice -voice) and cross-modal (voice-face)	**ASD < TD**: anger and neutral (unimodal); neutral (cross-modal)
Grossman and Tager-Flusberg (2012)	- *n* = 22 (18:4) - M_{age} = 13 yr, 10 mo (2 yr, 10 mo) - HFA	- *n* = 22 (19:3) - M_{age} = 14 yr, 0 mo (2 yr, 5 mo) - TD - Match on FSIQ, VIQ, PIQ	Anger, happiness, sadness, surprise	Stimuli: emotional prosody (low or high intensity) in sentences with neutral verbal content Task: cross-modal matching (prosody to photos of emotional faces)	**ASD < TD**: more ASD difficulty for differentiating same-valence emotions (happy vs surprise; anger vs. sadness) regardless of cue intensity **ASD < TD**: more ASD difficulty for identifying emotions with low vs. high intensity

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
Heaton et al. (2012)	- *n* = 20 (15:5) - M_{age} = 33.70 (12.77) - HFA	- *n* = 20 (15:5) - M_{age} = 22.60 (12.06) - TD - Match on FSIQ, VIQ, PIQ	Anger, disgust, fear, happiness, sadness, surprise	Stimuli: emotional prosody in three-digit numbers; **vocal affect bursts** Task: forced- choice emotion labelling	**ASD < TD**: total emotion (in prosody and vocal affect bursts) **ASD < TD**: more ASD difficulty for identifying vocal affect bursts vs. prosody Group difference partly accounted for by higher alexithymia in ASD
*Charbonneau et al. (2013)	- *n* = 32 (30:2) - M_{age} = 21.0 (6.0) - HFA	- *n* = 18 (all males) - M_{age} = 21.0 (4.0) - TD - Match on FSIQ, VIQ, PIQ	Disgust, fear	Stimuli: **vocal affect bursts** Task: same/different emotion judgments for unimodal (voice-voice) and cross-modal (voice-face); accuracy and RT	**ASD < TD**: total emotion for unimodal and cross-modal tasks (accuracy and slower RT)
Le Sourn-Bissaoui et al. (2013)	- *n* = 26 (all male) - M_{age} = 12.60 (2.50) - AS/HFA	- *n* = 26 (all male) - M_{age} = 12.10 (2.60) - TD - Match on VIQ	Positive and negative valence (no specific emotion)	Stimuli: emotional prosody in meaningless utterances, presented with or without congruent/discrepant contextual visual information Task: cross-modal matching (prosody with/ without contextual information to smiling/crying face)	**ASD < TD**: positive emotions (in discrepant context) **ASD = TD**: total emotions (without context)

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
*Stewart et al. (2013)	- *n* = 11 (7:4) - M_{age} = 27.2 (7.5) - HFA/AS	- *n* = 14 (8:6) - M_{age} = 26.4 yr (5.6) - TD - Match on VIQ	Anger, disgust, fear, happiness, surprise	Stimuli: emotional prosody in sentences (with emotional or neutral verbal content); "mmm" (no verbal content) Task: forced-choice emotion labelling	**ASD < TD**: neutral (that is incongruent with verbal content); neutral "mmm"
Oerlemans et al. (2014)	- *n* = 66 (80-83% male; 30 with ADHD, 36 without ADHD) - M_{age} = 11.5-11.6 (1.2-1.5) - HFA	- *n* = 72 (87% male) - M_{age} = 10.7 yr (1.1) - TD - Match on FSIQ, VIQ, PIQ	Anger, fear, happiness, sadness	Stimuli: emotional prosody in sentences with neutral verbal content Task: free-choice emotion labelling (accuracy and RT)	**ASD (with and without ADHD) < TD**: sadness (accuracy); anger, fear, happiness, sadness (slower RT) **ASD (with ADHD) < TD**: sadness (accuracy)
*Globerson et al. (2015)	- *n* = 23 (all males) - M_{age} = 26.2 yr (3.5) - HFA	- *n* = 21 (all males) - M_{age} = 28.8 yr (6.8) - TD - Match on receptive vocabulary scores	Anger, fear, happiness, sadness, neutral	Stimuli: emotional prosody (of low and high intensity) in utterances with neutral verbal content (e.g., sentences, "nonsense" mono/ polysyllabic words) Task: forced-choice emotion labelling Other task: sensitivity to "stress" in linguistic prosody and how it alters the intended meaning of the sentence (focus-perception task)	**ASD < TD**: total emotion (deficit more pronounced in less intense emotions) **ASD = TD**: linguistic prosody perception

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
*Taylor et al. (2015)	Two groups ALI (impaired language): - *n* = 12 (10:2) - M_{age} = 92.75 mo (23.01) ALN (normal language): - *n* = 17 (12:5) - M_{age} = 116.0 mo (26.97)	Two groups SLI (specific language impairment): - *n* = 18 (15:3) - M_{age} = 88.17 mo (16.58) TD: - *n* = 53 (26:28) - M_{age} = 107.31 mo (23.01)	Basic: anger, fear, happiness, sadness Complex: disgust, surprise (as classified by the authors)	Stimuli: emotional prosody in sentences with neutral verbal content Task: cross-modal matching (prosody to cartoon faces; RT and accuracy)	**ALI < TD**: total emotion accuracy (basic and complex) **ALN < TD**: total emotion accuracy (complex) **ASD (both groups) = TD**: total emotion RT (basic and complex) SLI showed similar profile of emotion recognition to ASD, except SLI < TD for total emotions (basic) – slower RT
Wang and Tsao (2015)	- *n* = 25 (all males) - M_{age} = 97.84 mo (14.01) - HFA	- *n* = 25 (all males) - M_{age} = 98.36 mo (12.49) - TD - Match on FSIQ, PIQ	Anger, happiness, sadness	Stimuli: emotional prosody in words and short sentences (with emotional or neutral verbal content) Task: cross-modal matching (prosody to cartoon faces)	**ASD < TD**: happiness (regardless of whether congruent/ incongruent with verbal content)
*Xavier et al. (2015)	- *n* = 19 (14:5) - M_{age} = 9.95 (1.75) - HFA	- *n* = 19 (14:5) - M_{age} = 8.84 (1.79) - TD	Anger, fear, disgust, happiness ("joy"), sadness, neutral	Stimuli: **vocal affect bursts** Task: forced-choice emotion labelling; cross-modal matching (voices to facial emotions)	**ASD = TD**: on unimodal and cross-modal tasks

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
*Fridenson-Hayo et al. (2016)	Three groups (all HFA) Israel: - *n* = 20 (18.2) - M_{age} = 7.45 (1.31) Britain: - *n* = 16 (15.1) - M_{age} = 8.58 (1.03) Sweden: - *n* = 19 (15.4) - M_{age} = 6.97 (0.67)	Three control groups (each matched on VIQ, PIQ with respective ASD group) Israel: - *n* = 22 (19.3) - M_{age} = 7.50 (1.47) Britain: - *n* = 18 (13.5) - M_{age} = 7.80 (1.42) Sweden: - *n* = 18 (15.3) - M_{age} = 7.36 (1.2)	Anger, disgust, fear, happiness, sadness, surprise	Stimuli: emotional prosody in sentences with neutral verbal content Task: forced-choice emotion labelling Other Task: forced-choice emotion labelling for emotional prosody representing six complex emotions	**ASD < TD**: total emotion (basic and complex) across cultures
Ketelaars et al. (2016)	- *n* = 31 (all females) - M_{age} = 41.35 (11.22) - HFA	- *n* = 28 (all females) - M_{age} = 39.80 (13.20) - TD	Anger, fear, happiness, sadness	Stimuli: emotional in sentences with neutral verbal content Task: forced-choice emotion labelling (RT and accuracy)	**ASD = TD**: total emotion accuracy **ASD < TD**: total emotion slower RT (not influenced by level of alexithymia in ASD
Matsumoto et al. (2016)	- *n* = 12 (6:6) - M_{age} = 11.83 (1.9) - HFA	- *n* = 12 (6:6) - M_{age} = 11.58 (1.68) - TD - Match on FSIQ, VIQ, PIQ	Anger, happiness, neutral	Stimuli: emotional prosody in sentences and words with neutral verbal content Task: forced-choice emotion labelling (RT and accuracy)	**ASD < TD**: total emotion in words and sentences (slower RT) **ASD = TD**: total emotion in words and sentences (accuracy)

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
				Other task: semantic task – pick illustration that matches verbal content in sentences and words	**ASD < TD**: on semantic task when verbal content was paired with angry prosody
*Tobe et al. (2016)	- *n* = 19 (17:2) - M_{age} = 37.8 (10.4) - HFA	Two groups Schizophrenia: - *n* = 92 (79:13) - M_{age} = 39.4 (12.5) TD: - *n* = 73 (45:28) - M_{age} = 36.0 (11.8) - Match on highest level of education achieved	Anger, fear, happiness, sadness, neutral	Stimuli: emotional prosody (varies in intensity) in sentences with neutral verbal content Task: rate emotional category and intensity Other task: ToM (identify sarcasm in attitudinal prosody in sentences with neutral verbal content)	**ASD = TD**: total emotion **ASD < TD:** ToM **ASD > Schizophrenia**: total emotion, ToM
Chiew and Kjelgaard (2017)	- *n* = 13 (12:1) - M_{age} = 11 yr, 7 mo (1 yr, 0 mo) - HFA	- *n* = 21 (8:13) - M_{age} = 8 yr, 0 mo (5 mo) - TD	Anger, happiness, "in the middle"	Stimuli: emotional prosody in filtered sentences Task: forced-choice emotion labelling (RT and accuracy)	**ASD < TD**: total emotion (accuracy and slower RT)
*Golan et al. (2018)	- *n* = 29 (24:5) - M_{age} = 9.13 (1.18) - ID	- *n* = 34 (27:7) - M_{age} = 4.01 (1.11) - TD - Match on verbal mental age	Anger, happiness, sadness, surprise	Stimuli: **vocal affect bursts**, Task: cross-modal matching (voice to emotional faces) Other task: cross-modal matching for face-face, word label-face	**ASD < TD**: total emotion (across all cross-modal matching conditions) **ASD < TD**: more ASD difficulty recognising surprise and anger vs. happiness and sadness

Reference	ASD *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Controls *n* (male: female), $M_{age\ in\ years}$ (*SD*)	Emotions	Stimuli and Task	[a] Group Differences in Recognition
					(across all cross-modal matching conditions)
*Schelinski and von Kriegstein (2019)	- *n* = 16 (13:3) - M_{age} = 33.75 (10.12) - HFA	- *n* = 16 (13:3) - M_{age} = 33.69 (9.58) - TD	Anger, disgust, fear, happiness, sadness, neutral	Stimuli: emotional prosody in sentences with neutral verbal content Task: forced-choice emotion labelling	**ASD < TD**: sadness and fear

Note. Asterisks (*) indicate studies that also include additional tasks (not pertaining to the recognition of emotional voices), that are not described here. For example, some studies also assessed the recognition of emotions in faces, body postures, or situational contexts; or emotion production, object recognition, pitch perception, and linguistic processing. Asterisks also indicate studies that assess additional clinical groups besides ASD, that are not described in the table. HFA = High-functioning autism; LFA = low-functioning autism; AS = Asperger's Syndrome; TD = typically-developing; ID = intellectual disability; LFC = low-functioning controls; HFC = high-functioning controls.

[a] Group differences significant at $p < .05$, $p < .01$, or $p < .001$

[b] Total emotion refers to composite score of all emotions tested, as per main effect for group in ANOVA

Appendix D

MNI Coordinates of Peak Voxels (Uncorrected Threshold) from the RFX Analysis of the "ASD > Controls" Contrast in Study 1

This appendix lists the MNI coordinates and T-scores for peak voxels that showed a trend towards higher activation in the ASD group versus controls under the RFX analysis in Study 1 (Chapter 5). Of note, activation in these voxels were only significant at an uncorrected voxel-wise threshold of $p < .001$, but were not significant at a cluster-wise FWE-corrected threshold ($p < .05$).

Table D.1

Whole-Brain RFX Analysis: Peak Voxels with Higher Activation for the ASD Group versus Controls at an Uncorrected Voxel-Wise Threshold

Region	*x*	*y*	*z*	T-score
R inferior frontal gyrus (opercularis)*	36	11	20	4.02
R postcentral gyrus	57	-1	17	3.88
R lingual gyrus	12	-40	-4	3.45
L cerebellum (VI)	-36	-37	-28	3.77
L medial orbitofrontal gyrus	-9	53	-13	3.60
R insula	39	-10	5	3.58
L inferior temporal gyrus	-51	-43	-10	3.54
R hippocampus	24	-34	-4	3.53
R postcentral gyrus	48	-19	38	3.49
R precentral gyrus*	27	-10	50	3.48

Note. Results are from the "ASD > controls" T-contrast, thresholded at a voxel-wise level of $p < .001$ (uncorrected). The table shows MNI coordinates and T-scores from each peak voxel. Peak voxels are separated by more than 8 mm. Peak voxels are labelled according to the AAL atlas (Tzourio-Mazoyer et al., 2002). Asterisks (*) indicate the approximate region for peak voxels that do not have a corresponding label from the AAL atlas. L = left; R = right.

Appendix E

MNI Coordinates of Peak Voxels from the FFX Analyses of Activation Within and Between the ASD and Control Groups in Study 1

This appendix contains two tables listing the MNI coordinates and T-scores for peak voxels from the FFX analyses of (a) the "emotion > baseline" contrast within the ASD and control groups, and (b) the "ASD > controls" between-group contrast from Study 1 (Chapter 5). All analyses were performed at a cluster-wise corrected significance threshold, as specified in the "Note" section at the bottom of each table.

Table E.1
Whole-Brain FFX Analyses: Peak Voxels in Significant Clusters of the ASD and Control Groups

	Local maxima				
Cluster Size (*k*)	Region	*x*	*y*	*z*	T-score
ASD					
6308	L lingual gyrus	-12	-85	2	7.81
	R calcarine sulcus	18	-91	5	7.56
	R cerebellum (Cr II)	12	-79	-34	7.27
	L inferior occipital gyrus	-42	-67	-13	6.76
	L middle temporal gyrus	-54	-55	8	6.58
	L middle occipital gyrus	-33	-94	11	6.53
	L cerebellum (VI)	-6	-79	-16	6.21
	R middle occipital gyrus	42	-88	-1	6.16
1361	L inferior frontal gyrus (triangularis)	-48	23	20	7.36
	L precentral gyrus	-33	8	29	7.29
	L superior temporal pole	-51	20	-13	6.31
	L middle frontal gyrus	-48	44	29	5.53
	L middle temporal gyrus	-54	2	-16	5.16
	L inferior frontal gyrus (orbitalis)	-51	44	-4	4.80
423	R middle frontal gyrus	57	26	32	5.81
	R inferior frontal gyrus (triangularis)	48	26	20	5.66
	R putamen	27	17	-1	4.48
	R inferior frontal gyrus (orbitalis)	51	26	-7	4.31
	R insula*	36	14	-4	4.30
	R precentral gyrus	57	11	41	4.24
312	R middle temporal pole	54	5	-19	5.44
	R middle temporal gyrus	48	-13	-13	5.29
	R superior temporal gyrus	54	-37	11	4.83
125	R angular gyrus	30	-61	38	5.09

	Local maxima				
Cluster Size (*k*)	Region	*x*	*y*	*z*	T-score
121	L middle cingulum	-9	20	35	4.56
	L supplementary motor area	-6	8	50	4.07
	R supplementary motor area	3	8	59	3.88
115	L amygdala	-24	-4	-25	4.68
	L hippocampus	-18	-7	-13	4.57
	L putamen*	-30	-19	-7	3.95
92	R hippocampus*	33	-7	-13	4.71
	R amygdala	30	-1	-25	4.57
46	Vermis (IX)	0	-55	-37	4.48
	R cerebellum (IX)	9	-55	-43	4.18
	L cerebellum (IX)	-12	-52	-37	3.90
26	L superior temporal gyrus	-57	-13	-4	4.57
	L middle temporal gyrus	-48	-22	-7	3.89
Controls					
2092	R cerebellum (Cr II)	12	-79	-34	7.98
	R calcarine sulcus	18	-91	2	7.84
	L calcarine sulcus*	-12	-91	-1	7.38
	R cuneus	18	-94	11	7.30
	L inferior temporal gyrus	-42	-46	-13	7.30
	L inferior occipital gyrus	-39	-82	-4	6.29
	L lingual gyrus	-18	-85	-16	6.23
	R cerebellum (VIII)	30	-67	-49	5.90
	R cerebellum (VI)	21	-79	-22	5.28
	L cerebellum (Cr II)	-9	-76	-37	4.81
	L cerebellum (Cr I)	-6	-76	-28	4.76
1527	L inferior frontal gyrus (triangularis)	-45	29	5	9.45
	L precentral gyrus	-36	8	32	8.15
	L middle temporal gyrus	-57	-40	8	6.40
	L superior temporal pole	-51	11	-10	5.85
	L superior temporal gyrus	-57	-13	-4	5.35
619	R inferior frontal gyrus (triangularis)	54	29	2	7.04
	R precentral gyrus	51	8	47	5.46
	R inferior frontal gyrus (opercularis)	39	11	32	4.84
309	R middle temporal gyrus	51	-16	-10	7.38
	R superior temporal pole	48	17	-22	5.37
258	L inferior parietal gyrus	-24	-67	41	6.74
	L superior parietal gyrus	-27	-61	44	6.73
165	L superior frontal gyrus (medial)	0	23	50	5.52

	Local maxima				
Cluster Size (*k*)	Region	*x*	*y*	*z*	T-score
	R supplementary motor area	3	14	62	5.09
	L middle cingulum	-6	26	35	4.00
69	L thalamus	-3	-13	8	4.83
	R thalamus	6	-10	5	4.63

Note. Results are from the "emotion > baseline" T-contrast, thresholded at a cluster-wise FWE-corrected level of $p < .05$ (voxel-wise primary threshold of $p < .0001$). The table shows cluster size (*k*), along with MNI coordinates and T-scores from the three highest peak voxels from each structure within the cluster. Peak voxels are separated by more than 8 mm. Peak voxels are labelled according to the AAL atlas (Tzourio-Mazoyer et al., 2002). Asterisks (*) indicate the approximate region for peak voxels that do not have a corresponding label from the AAL atlas. L = left; R = right.

Table E.2

Whole-Brain FFX Analyses: Peak Voxels in Clusters of Significantly Higher Activation for the ASD Group versus Controls

	Local maxima				
Cluster Size (*k*)	Region	*x*	*y*	*z*	T-score
3103	L middle temporal gyrus	-51	-58	11	6.35
	L angular gyrus	-54	-70	23	5.34
	L middle occipital gyrus	-51	-79	8	5.00
	R middle temporal gyrus	51	-58	11	4.98
	L calcarine sulcus	0	-88	5	4.75
	L fusiform gyrus	-30	-67	-16	4.74
	R cerebellum (6)	18	-70	-28	4.73
	R inferior occipital gyrus	30	-82	-16	4.69
	Vermis (VI)	3	-70	-19	4.64
	L inferior occipital gyrus	-42	-67	-13	4.64
	R middle occipital gyrus	39	-67	8	4.59
	Vermis (VII)	6	-73	-25	4.52
348	L fusiform gyrus	-24	-31	-25	4.38
	L hippocampus	-21	-7	-25	4.28
	L middle temporal gyrus	-48	-1	-22	4.19
	L middle temporal pole	-48	11	-28	4.09
	L cerebellum (VI)	-33	-40	-34	3.78
	L parahippocampal gyrus	-24	-37	-13	3.28
181	L inferior frontal gyrus (triangularis)	-39	26	14	4.30
	L middle frontal gyrus	-39	29	29	3.80
	L inferior frontal gyrus (opercularis)	-36	14	20	3.47
139	R hippocampus	30	-16	-19	4.39
	R parahippocampal gyrus	27	-1	-37	3.41
	R cerebellum (IV, V)	24	-31	-25	3.25
129	R precentral gyrus	39	-13	56	3.92
85	R rolandic operculum*	48	-22	23	3.91
	R superior temporal gyrus	57	s-31	20	3.52
	R postcentral gyrus	54	-13	29	3.43

Note. Results are from the "ASD > controls" T-contrast, thresholded at a cluster-wise FWE-corrected level of $p < .05$ (voxel-wise primary threshold of $p < .001$). The table shows cluster size (*k*), along with MNI coordinates and T-scores from the three highest peak voxels from each structure within the cluster. Peak voxels are separated by more than 8 mm. Peak voxels are labelled according to the AAL atlas (Tzourio-Mazoyer et al., 2002). Asterisks (*) indicate the approximate region for peak voxels that do not have a corresponding label from the AAL atlas. L = left; R = right.

Appendix F

Procedure for Creating ROI Masks of Emotional Voice Areas that Were Activated by the ASD Group in Study 1

This appendix outlines the steps that were taken to create inclusive ROI masks of regions within the bilateral IFG (pars opercularis and triangularis), left STS/MTG, and right STS/MTG/STG that were activated by the ASD group in Study 1 (Chapter 5). Activation in these regions were deemed significant under the whole-brain RFX analysis of the "emotion > baseline" T-contrast, thresholded at a cluster-wise FWE-corrected level of $p < .05$, (voxel-wise primary threshold of $p < .001$). The ROI masks were used to extract mean parameter estimates (i.e., average of beta values across all voxels in the mask) from each ASD participant's contrast image. Correlational analyses were then performed to determine the relationship between the mean parameter estimates in each ROI and informant-ratings of symptom severity on the SRS-2.

Procedure:

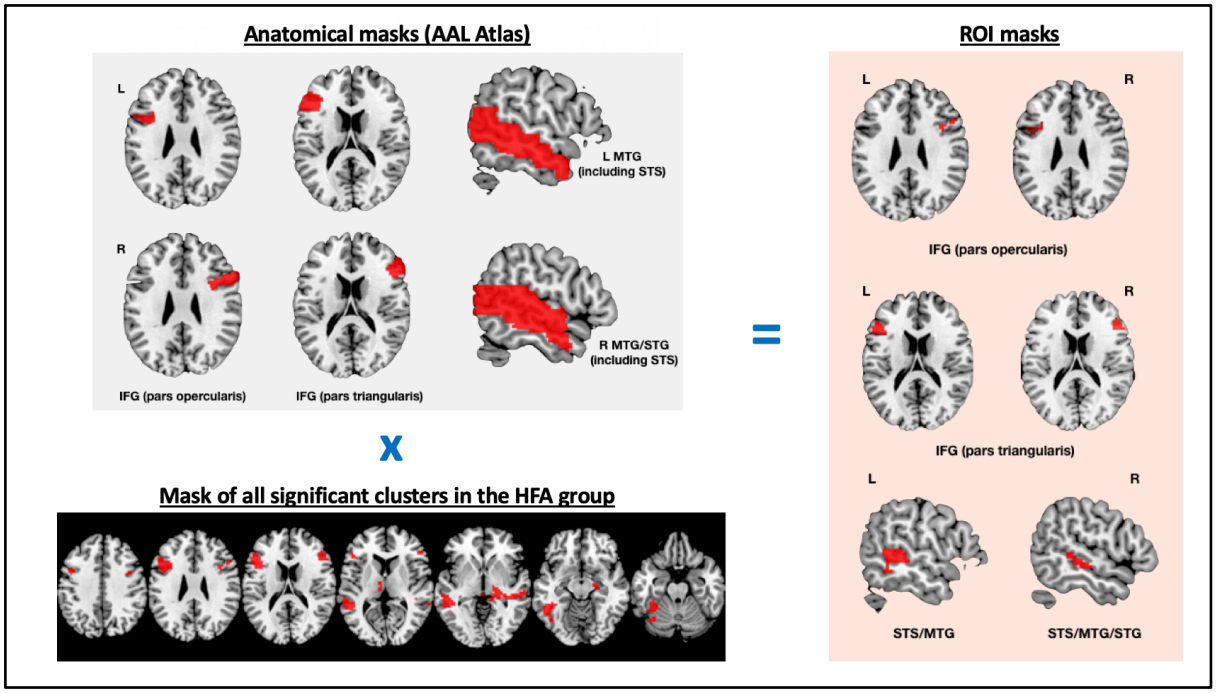
1. Create anatomical masks of the following regions using the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) via the WFU_PickAtlas toolbox for SPM (Maldjian, Laurienti, Kraft, & Burdette, 2003):

    - Left IFG pars opercularis
    - Right IFG pars opercularis
    - Left IFG pars triangularis
    - Right IFG pars triangularis
    - Left MTG (inclusive of STS)
    - Right MTG + STG (inclusive of STS)



*Note that separate masks were created for each anatomical region, with the exception of masks for the right MTG and right STG, which were combined into a single STG/MTG mask (inclusive of the STS)

2. Multiply each anatomical mask from Step 1 with a single mask of all significant clusters (across the whole brain) in the ASD group using the Image Calculator in SPM. The resultant "ROI masks" should only include the regions of significant brain activation that "overlap" with the anatomical masks.



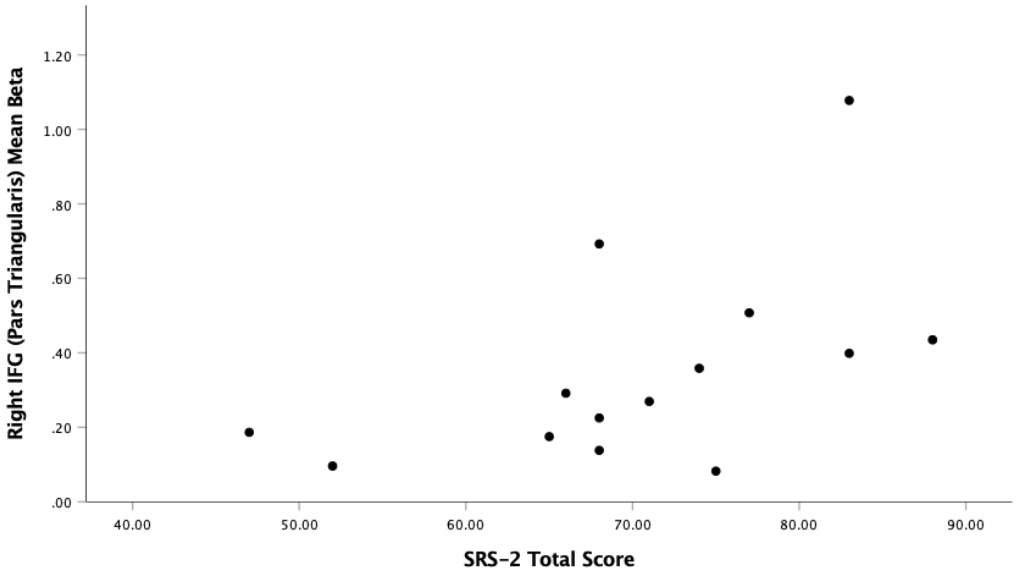
*The red markings in this figure represent each inclusive mask. Masks are shown overlaid on axial and sagittal T1-weighted images in MNI space. L = left; R = right.

Appendix G

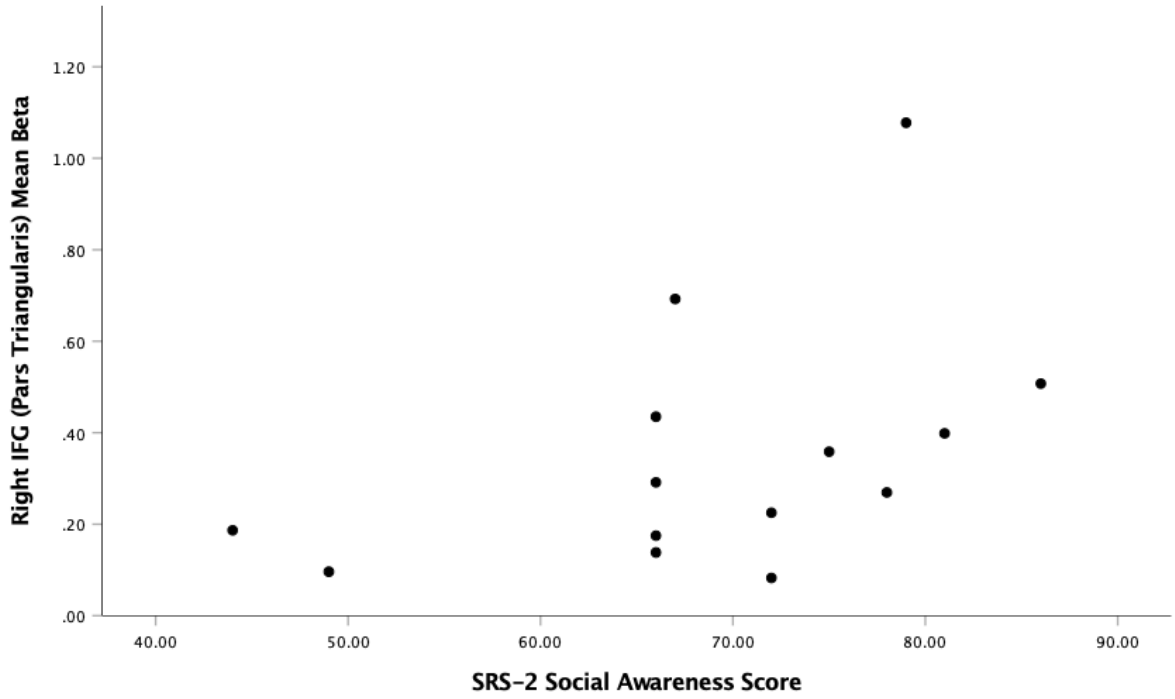
Scatterplots Showing the Relationship Between Activity in the Bilateral IFG and Symptom Severity for the ASD group in Study 1

This appendix contains five scatterplots showing the significant monotonic relationship between mean parameter estimates (beta values) of regions-of-interests (ROIs) within the bilateral IFG and informant ratings (symptom severity scores) on selected SRS-2 scales for participants with ASD (n = 14) from Study 1 (Chapter 5). A regression line was not presented with each scatterplot, since the relationship between variables was analysed using Spearman's rank-ordered correlation coefficients.

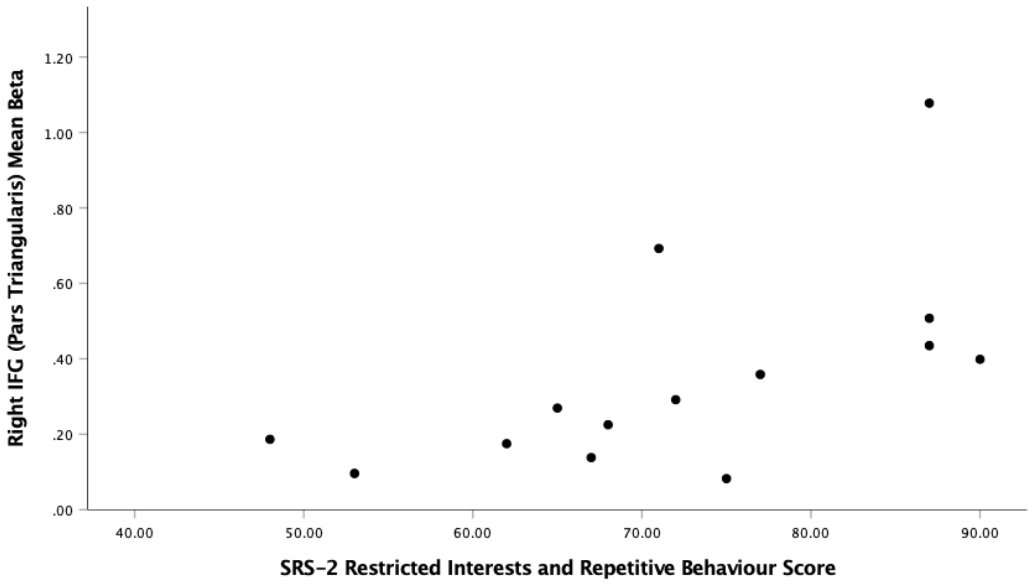
(a) Right IFG (Pars Triangularis) and Total Score: $r_s(12) = .58$, $p = .031$



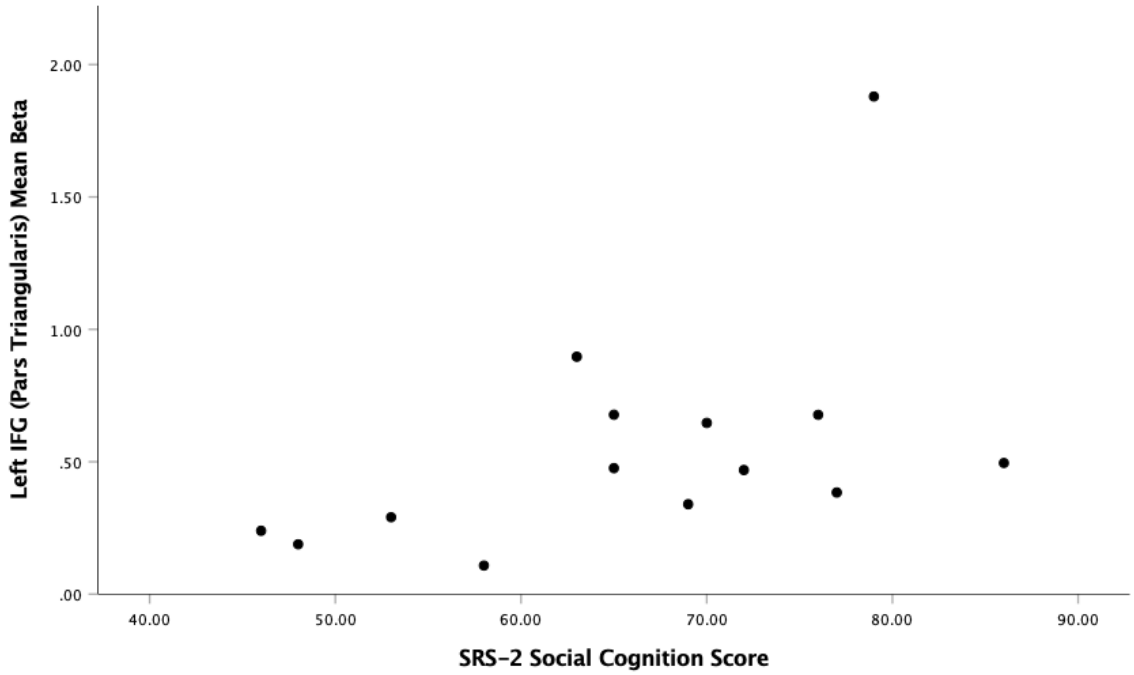
(b) <u>Right IFG (Pars Triangularis) and Social Awareness:</u> $r_s(12) = .54$, $p = .045$



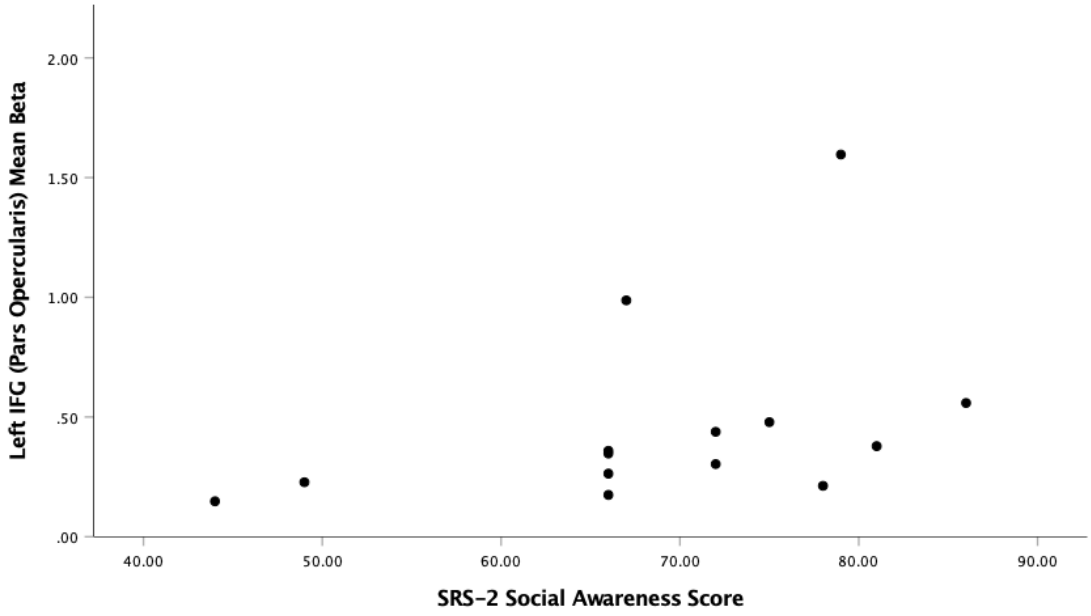
(c) <u>Right IFG (Pars Triangularis) and Restricted Interests and Repetitive Behaviour</u>: $r_s(12) = .66$, $p = .010$



(d) <u>Left IFG (Pars Triangularis) and Social Cognition:</u> $r_s(12) = .58$, $p = .030$



(e) <u>Left IFG (Pars Opercularis) and Social Awareness</u>: $r_s(12) = .64$, $p = .014$



APPENDIX H

CATS Protocol for Identifying BAP Status in ASD-Relatives from Study 2

This appendix describes the standard protocol used by the Collaborative Autism Study (CATS; University of Melbourne) to identify BAP-positive status in relatives of individuals with ASD. This description is summarised from an article published by other researchers from the CATS team (Trevis et al., 2019)[2], which introduces a novel phenotyping procedure for detecting the BAP in relatives.

Relatives enrolled in the CATS (including family members from Study 2 [Chapter 6])[3] were assigned BAP-positive status if they met criteria (cut-off scores) for at least one of four behavioural markers of the BAP: (i) socially unaware, (ii) aloof, (iii) pedantic, and (iv) obsessive. The following steps were used to delineate these BAP markers and their cut-off scores in Trevis et al. (2019). The steps are divided into three phases:

Phase 1: Identifying an exhaustive list of BAP traits

1) Family members ($N = 47$) from two large multiplex ASD families were assessed on an extensive battery of quantitative and qualitative measures (Table H.1).

[2] Citation: Trevis, K. J., Brown, N. J., Green, C., Lockhart, P., Hickey, P., Fanjul-Fernández, M., . . . Wilson, S. J. (2019). Tracing Autism Traits in Large Multiplex Families to Identify Endophenotypes of the Broader Autism Phenotype. *bioRxiv*, 659722. doi:10.1101/659722

[3] As acknowledged in the Preface, other members of the CATS team (not the PhD candidate) were responsible for assessing the BAP in all relatives from Study 2 (Chapter 6).

Table H.1

Measures Administered to Family Members enrolled in the CATS

Measure	Reference
Family History Interview	Bolton et al. (1994)
Broader Autism Phenotype Rating Scale	Adapted from Bailey et al. (1995)
Pragmatic Rating Scale	Landa et al. (1992)
Faux Pas Task (modified adult version)	Stone, Baron-Cohen, and Knight (1998)
Goldman-Eisler Cartoon Task ("Cowboy Story" for assessment of discourse/narrative)	Goldman (1968); Joanette and Goulet (1990)
Adaptive Behaviour Assessment System – Second Edition	Harrison and Oakland (2003)
Behaviour Rating Inventory of Executive Function	Gioia, Isquith, Guy, and Kenworthy (2000)
Delis Kaplan Executive Function System (selected subtests)	Delis, Kaplan, and Kramer (2001)
Wechsler Abbreviated Scale of Intelligence (WASI, WASI-II)	Wechsler (1999, 2011)

2) Three clinicians with expertise in neurodevelopmental disorders (i.e., neuropsychologist [Prof Sarah Wilson], paediatric neurologist [Prof Ingrid Scheffer], paediatrician [Dr Natasha Brown]) identified 33 BAP traits (Table H.2.), based on information provided on interview and their observation of the participants' behavior on testing. These traits reflect broader theoretical domains of the BAP (i.e., impaired reciprocal social interaction, communication deficits, and repetitive or restricted behaviours/interests) proposed by Bolton et al. (1994).

Table H.2

List of 33 BAP Traits Identified by Trevis et al. (2019)

BAP Domains (Bolton et al., 1994)	BAP Traits (Trevis et al., 2019)
Social communication (pragmatics and relationships)	• Tangential pragmatic style • Making inappropriate or awkward comments either on history or during assessments • Tendency to monologue rather than participate in reciprocal conversation • An unusual or awkward greeting style • Terse pragmatic style • Overly technical language • A limited capacity to develop rapport with assessors • Opinionated in conversation • Little appreciation of humour during cartoon task • Tendency to anger easily • Unusual eye gaze • Narcissistic personality style • Self-perception incongruent with views of others • Aloof personality style • Difficult or limited interpersonal relationships • Reduced emotional empathy • Reduced affection • Awkward social interactions • Reduced cognitive empathy • Excessive worry
Communication (speech and literacy)	• Reduced capacity for clear narrative • Difficulty answering open ended questions • Reduced quantity of verbal output • Speech has little variation in tone (i.e. monotonous) • Unusual speech volume • Precise articulation and language
Circumscribed interests	• Recurrent thoughts • Focus on technicalities or minutiae • Fastidious regarding personal appearance • Hobby or interest of unusual intensity, or restricted range of interests relative to peers • Large collections or hoarding of items • Fastidious cleaning • Preference for structure in activities of daily living

Phase 2: Clustering BAP traits into more homogenous sub-groups

3) The 33 BAP traits were applied to an independent sample of 45 family members from 20 smaller ASD families, who completed the battery of tests listed in Table H.1. A post-doctoral research fellow with expertise in ASD assessment (Dr Cherie Green) rated participants for severity (*0 = absent* to *3 = severe*) on each of the 33 BAP traits. Ratings were based on the participant's developmental history and the examiner's observation of the participant's behaviour on testing.

4) A hierarchical cluster analysis (Ward's Method with Euclidean squared distances) was performed on severity ratings across the 33 BAP traits, in order to derive groupings of similar traits. **Four clusters were identified, corresponding to behavioural markers of the BAP (Table H.3).**

Table H.3
Behavioural Markers of the BAP Derived from a Cluster Analysis of 33 BAP Traits (Trevis et al., 2019)

BAP Marker	Description	BAP Traits
Socially unaware	Poor self-regulation and reciprocity in conversation *Cut-off score > 0.17*	• Reduced capacity for clear narrative • Difficulty answering open-ended questions • Making inappropriate or awkward comments either on history or during assessments • Tangential pragmatic style • Tendency to monologue rather than participate in reciprocal conversation • Tendency to anger easily • Reduced quantity of verbal output *Maximum severity score: 21 (7 traits x 3)*

BAP Marker	Description	BAP Traits
Pedantic	Self-focused and technical in interactions *Cut-off score > 0.14*	• Unusual or awkward greeting style • Little variation in tone of speech (i.e., monotonous) • Unusual eye gaze • Unusual speech volume • Precise articulation and language • Terse pragmatic style • Overly technical language • Narcissistic personality style • Focus on technicalities or minutiae • Self-perception incongruent with views of others • Fastidious regarding personal appearance *Maximum severity score: 33 (11 traits x 3)*
Aloof	Difficulty relating to others' emotions and expressing one's own emotions *Cut-off score > 0.20*	• Aloof personality style • Difficult or limited interpersonal relationships • Reduced emotional empathy • Limited capacity to develop rapport with assessors • Reduced affection • Awkward social interactions • Opinionated in conversation • Reduced cognitive empathy • Little appreciation of humour during cartoon task *Maximum severity score: 27 (9 traits x 3)*
Obsessive	Regimented approach to life and tendency to ruminate *Cut-off score > 0.25*	• Hobby or interest of unusual intensity, or restricted range of interests relative to peers • Large collections or hoarding of items • Fastidious cleaning • Preference for structure in activities of daily living • Recurrent thoughts • Excessive worry *Maximum severity score: 18 (6 traits x 3)*

Phase 3: Deriving cut-off scores for behavioural markers of the BAP

5) A proportional score per cluster was calculated for each participant. Specifically, severity scores on each trait (range 0-3) were summed and divided by the maximum severity score for that cluster (Table H.3).

6) A ROC curve of proportional scores was plotted for each cluster. This enabled the calculation of optimum cut-off scores per cluster. **All participants with a proportional score above the cluster-specific cut-off score were determined to have a behavioural marker of the BAP (i.e., BAP-positive status).**

Appendix I

MNI Coordinates of Peak Voxels (Uncorrected Threshold) from the RFX Analysis of the "BAP > Controls" Contrast in Study 2

This appendix lists the MNI coordinates and T-scores for peak voxels that showed a trend towards higher activation in the BAP group versus controls, as revealed by the RFX analysis in Study 2 (Chapter 6). Of note, activation in these voxels were only significant at an uncorrected voxel-wise threshold of $p < .001$, but were not significant at a cluster-wise FWE-corrected threshold ($p < .05$).

Table I.1

Whole-Brain RFX Analysis: Peak Voxels with Higher Activation for the BAP Group versus Controls at an Uncorrected Voxel-Wise Threshold

Region	*x*	*y*	*z*	T-score
L fusiform gyrus	-27	-70	-7	4.26
L calcarine sulcus	-12	-73	20	3.95
L middle occipital gyrus	-36	-79	20	3.68

Note. Results are from the "BAP > controls" T-contrast, thresholded at a voxel-wise level of $p < .001$ (uncorrected). The table shows MNI coordinates and T-scores from each peak voxel. Peak voxels are separated by more than 8 mm. Peak voxels are labelled according to the AAL atlas (Tzourio-Mazoyer et al., 2002). L = left; R = right.

Appendix J

MNI Coordinates of Peak Voxels from the FFX Analyses of Activation Within the BAP and Control Groups in Study 2

This appendix lists the MNI coordinates and T-scores for peak voxels from the FFX analyses of the "emotion > baseline" contrast within the BAP and control groups from Study 2 (Chapter 6). All analyses were performed at a cluster-wise FWE-corrected significance threshold of $p < .05$ (voxel-wise primary threshold of $p < .0001$).

Table J.1

Whole-Brain FFX Analyses: Peak Voxels in Significant Clusters of the BAP and Control Groups

	Local maxima				
Cluster Size (*k*)	Region	*x*	*y*	*z*	T-score
BAP Group					
2847	R cerebellum (Crus I)	9	-76	-28	8.88
	L superior parietal gyrus	-27	-61	44	8.36
	L calcarine sulcus	-9	-91	-1	7.48
	L fusiform gyrus	-45	-58	-16	6.95
	L cerebellum (VI)	-39	-67	-22	6.66
	L inferior occipital gyrus	-30	-82	-13	6.50
	L cerebellum (Crus I)	-6	-76	-25	6.34
	L middle occipital gyrus	-33	-85	11	5.99
	R fusiform gyrus	27	-79	-16	5.11
	R cerebellum (VIIb)	36	-70	-49	5.08
	L precuneus	-6	-73	44	4.86
	L superior occipital gyrus	-18	-85	38	4.84
	R cerebellum (VIII)	36	-61	-52	4.64
1615	L inferior frontal gyrus (triangularis)	-48	23	23	9.49
	L inferior frontal gyrus (orbitalis)	-51	20	-7	6.74
	L middle frontal gyrus	-42	47	8	6.32
	L insula	-33	23	-4	5.82
458	L supplementary motor area	-3	17	44	6.22
412	R inferior frontal gyrus (opercularis)	54	20	35	7.09
	R inferior frontal gyrus (triangularis)	54	23	29	6.81
	R middle frontal gyrus*	48	8	56	5.14
200	R angular gyrus	33	-58	47	6.59
	R superior occipital gyrus	27	-64	35	5.11
131	L middle temporal gyrus	-51	-40	5	5.38
105	R inferior frontal gyrus (orbitalis)	42	29	-4	4.89

	Local maxima				
Cluster Size (*k*)	Region	*x*	*y*	*z*	T-score
	R insula	33	23	2	4.52
39	R middle cingulum	3	-31	29	5.00
Control Group					
3427	L calcarine sulcus	-6	-94	5	9.33
	R cerebellum (Crus I)	12	-76	-28	8.86
	R cerebellum (Crus II)	9	-79	-31	8.7
	L fusiform gyrus	-21	-82	-19	8.62
	R cerebellum (VIIb)	30	-73	-46	8.07
	L cerebellum (Crus I)	-6	-76	-28	7.91
	R cerebellum (VI)	33	-70	-25	7
	R calcarine sulcus	12	-88	-1	6.77
	L inferior temporal gyrus	-48	-52	-16	6.76
	L middle temporal gyrus	-57	-43	-7	6.75
	R fusiform gyrus	30	-73	-13	6.21
2030	L inferior frontal gyrus (triangularis)	-54	23	26	12.19
	L middle frontal gyrus	-45	50	5	8.75
	L precentral gyrus	-36	2	38	8.51
	L superior temporal pole	-51	8	-22	4.06
1061	R inferior frontal gyrus (triangularis)	54	26	29	9.67
	R insula	33	23	-4	7.06
	R precentral gyrus	42	5	41	5.58
782	L superior frontal gyrus (medial)	-3	26	47	9.83
	R middle cingulum	12	23	29	5.16
	R precentral gyrus	43	5	41	5.58
448	L superior parietal gyrus	-30	-64	44	9.46
190	R angular gyrus	30	-61	38	6.31
	R precuneus	15	-64	44	6.08
114	R middle temporal gyrus	51	-34	-1	5.88
69	R middle frontal gyrus	39	50	8	6.12
50	L splenium*	-3	-28	26	5.07
39	L precuneus	-6	-67	41	5.45
28	R middle temporal pole	57	8	-19	4.77
	R middle temporal gyrus	51	2	-22	4.11

Note. Results are from the "emotion > baseline" T-contrast, thresholded at a cluster-wise FWE-corrected level of $p < .05$ (voxel-wise primary threshold of $p < .0001$). The table shows cluster size (*k*), along with MNI coordinates and T-scores from the three highest peak voxels from each structure within the cluster. Peak voxels are separated by more than 8 mm. Peak voxels are labelled according to the Automated Anatomical Labelling atlas (AAL; Tzourio-Mazoyer et al., 2002). Asterisks (*) indicate the approximate region for peak voxels that do not have a corresponding label from the AAL atlas. L = left; R = right.

APPENDIX K

Behavioural Performance (By Sex) and Distribution of BAPQ Scores from Study 3

This appendix contains information about: (1) sex-specific behavioural data (emotion recognition accuracy and emotional intensity ratings; BAPQ scores), and (2) the distribution of BAPQ scores (across entire sample) of participants from Study 3 (Chapter 7). The table and figures below are included as "Online Resource 1" and "Online Resource 2", respectively, from the published manuscript in Chapter 7[4]:

Online Resource 1

Mean emotion recognition accuracy, emotion intensity ratings, and Broad Autism Phenotype Questionnaire (BAPQ) scores for males and females

	Male (n = 26)		Female (n = 35)	
	M (SD)	95% CI	*M (SD)*	95% CI
Accuracy (%)				
Total	80.19 (7.71)	[77.1, 83.37]	82.21 (6.48)	[79.95, 84.47]
Anger	72.44 (18.82)	[64.83, 80.04]	75.24 (15.32)	[69.97, 80.50]
Disgust	74.36 (21.72)	[65.59, 83.13]	79.52 (15.32)	[69.97, 80.50]
Fear	71.79 (20.96)	[63.33, 80.26]	68.57 (21.30)	[61.25 75.89]
Happiness	96.79 (8.19)	[93.49, 100.10]	98.57 (6.22)	[96.43, 100.71]
Sadness	90.38 (9.63)	[86.50, 94.27]	91.90 (8.45)	[89.00, 94.80]
Surprise	67.82 (22.76)	[53.63, 72.01]	70.48 (25.91)	[61.58, 9.38]
Intensity				
Total	137.88 (25.39)	[127.40, 148.36]	137.09 (25.44)	[128.21,145.97]
Anger	22.04 (6.64)	[19.36, 24.72]	21.94 (7.49)	[19.37, 24.52]
Disgust	19.73 (6.85)	[16.96, 22.50]	20.80 (6.86)	[18.44, 23.16]
Fear	23.12 (8.74)	[19.59, 26.64]	21.69 (8.02)	[18.93, 24.44]
Happiness	28.19 (5.58)	[25.94, 30.45]	28.37 (5.78)	[26.39, 30.36]
Sadness	30.15 (5.19)	[28.06, 32.25]	28.91 (6.02)	[26.85, 30.98]
Surprise	15.12 (6.65)	[12.43, 17.80]	15.11 (6.97)	[12.72, 17.51]
BAPQ				
Total	2.58 (0.48)	[2.39, 2.77]	2.50 (0.55)	[2.31, 2.69]
Aloof	2.70 (0.67)	[2.43, 2.97]	2.48 (0.79)	[2.20, 2.75]
Prag Lang	2.43 (0.58)	[2.19, 2.66]	2.47 (0.55)	[2.28, 2.65]
Rigid	2.62 (0.60)	[2.38, 2.86]	2.56 (0.66)	[2.34, 2.79]

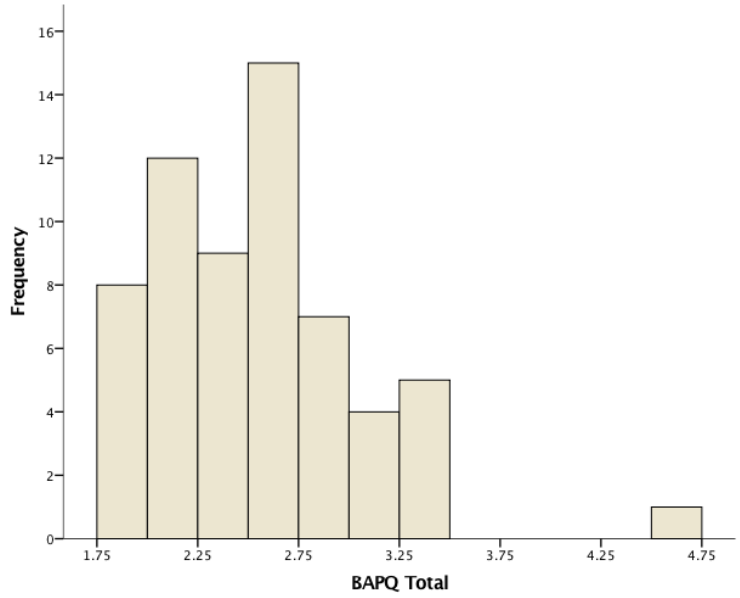
Note. Maximum intensity rating per emotion category is 42 points. Maximum score (self-rating) per BAPQ scale is 6 points. CI = confidence interval; Prag Lang = Pragmatic Language.

[4] Reference: Yap, V. M. Z., McLachlan, N. M., Scheffer, I. E., & Wilson, S. J. (2018). Enhanced Sensitivity to Angry Voices in People with Features of the Broader Autism Phenotype. *Journal of Autism and Developmental Disorders, 48*(11), 3899-3911. doi:10.1007/s10803-018-3641-7

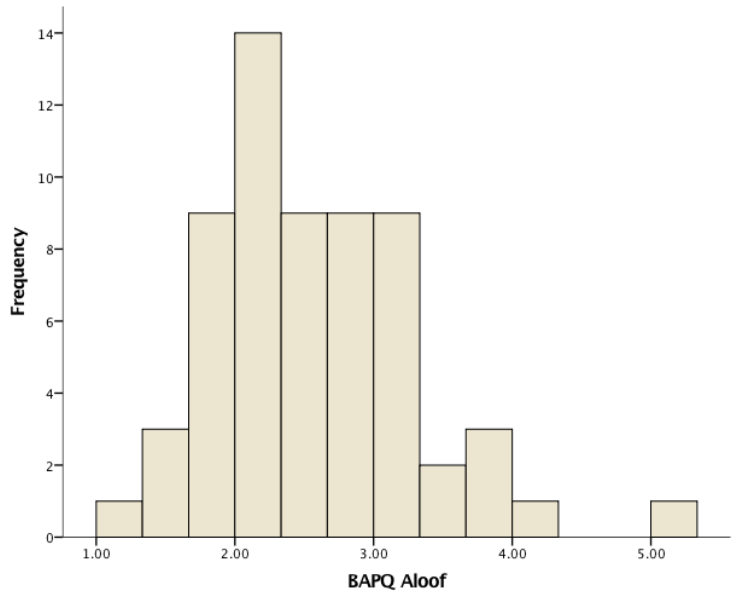
Online Resource 2

Distribution of self-ratings on the BAPQ across 61 participants: (a) Total score, (b) Aloof score, (c) Pragmatic Language score, and (d) Rigid score

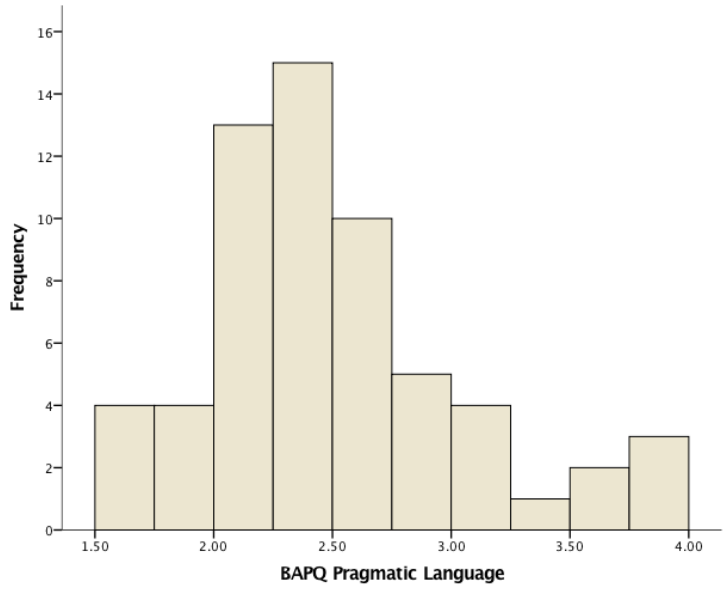
(a)



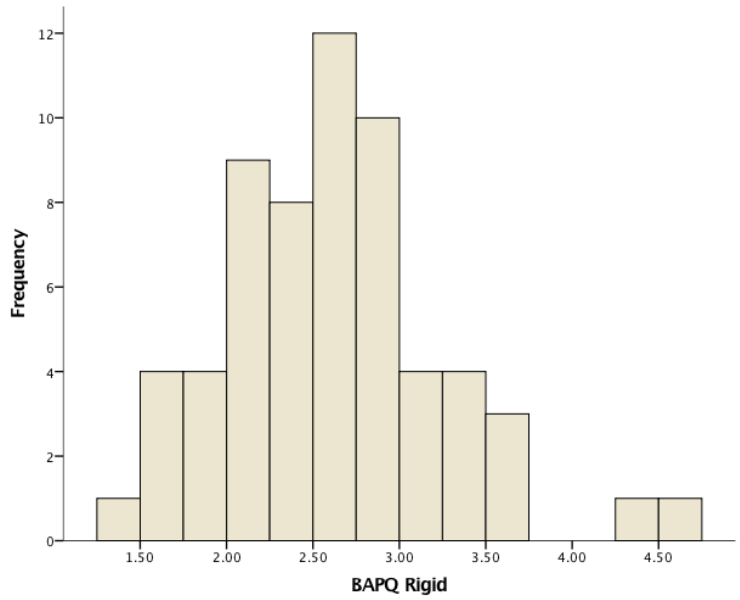
(b)



(c)


Frequency
16
14
12
10
8
6
4
2
0
1.50
2.00
2.50
3.00
3.50
4.00
BAPQ Pragmatic Language

(d)


Frequency
12
10
8
6
4
2
0
1.50
2.00
2.50
3.00
3.50
4.00
4.50
BAPQ Rigid